19th edition

Smith & Tanagho's
GENERAL UROLOGY

Jack W. McAninch • Tom F. Lue

McGraw Hill LANGE®

a LANGE medical book

Smith & Tanagho's General Urology

NINETEENTH EDITION

Edited by

Jack W. McAninch, MD, FACS, FRCS(E)(Hon)
Professor of Urology
University of California School of Medicine
Chief, Department of Urology
San Francisco General Hospital
San Francisco, California

Tom F. Lue, MD, FACS, ScD (Hon)
Professor of Urology
Department of Urology
University of California School of Medicine
San Francisco, California

Mc Graw Hill

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

Copyright © 2020 by McGraw-Hill Education. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-25-983434-9
MHID: 1-25-983434-4

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-983433-2,
MHID: 1-25-983433-6.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publica-tion. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the informa-tion contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

Contents

Contributors vii
Preface xi

1 Anatomy of the Genitourinary Tract 1

Emil A. Tanagho, MD; & Tom F. Lue, MD, ScD (Hon), FACS

2 Embryology of the Genitourinary System 17

Emil A. Tanagho, MD; Hiep T. Nguyen, MD; & Michael DiSandro, MD

3 Symptoms of Disorders of the Genitourinary Tract 31

Benjamin N. Breyer, MD, MAS, FACS

4 Physical Examination of the Genitourinary Tract 41

Maxwell V. Meng, MD, MPH; & Emil A. Tanagho, MD

5 Urologic Laboratory Examination 49

Anobel Y. Odisho, MD, MPH; Sima P. Porten, MD, MPH; & Kirsten L. Greene, MD, MS

6 Radiology of the Urinary Tract 63

Daniela Franz, MD; Scott Gerst, MD; & Hedvig Hricak, MD, PhD

7 Vascular Interventional Radiology 107

Ryan Kohlbrenner, MD; & Roy L. Gordon, MD

8 Retrograde Instrumentation of the Urinary Tract 117

Marshall L. Stoller, MD

9 Percutaneous Endourology and Ureterorenoscopy 129

David B. Bayne, MD, MPH; Joachim W. Thüroff, MD; Rolf Gillitzer, MD; & Thomas Chi, MD

10 Laparoscopic Surgery 149

David B. Bayne, MD, MPH; J. Stuart Wolf, Jr., MD, FACS; Marshall L. Stoller, MD; & Thomas Chi, MD

11 Robotic Surgery in Urology 167

Maxwell V. Meng, MD, MPH

12 Urinary Obstruction & Stasis 177

Marshall L. Stoller, MD; & Tom F. Lue, MD, FACS, ScD (Hon)

13 Vesicoureteral Reflux 191

Thomas W. Gaither, MD, MAS; & Hillary L. Copp, MD, MS

14 Bacterial Infections of the Genitourinary Tract 201

Mary K. Wang, MD; & Hillary L. Copp, MD, MS

15 Specific Infections of the Genitourinary Tract 229

Emil A. Tanagho, MD; & Christopher J. Kane, MD, FACS

16 Sexually Transmitted Infections 243

Kristin Madden, PharmD; Amanda B. Reed-Maldonado, MD, FACS; & John N. Krieger, MD

17 Urinary Stone Disease 259

Marshall L. Stoller, MD

18 Injuries to the Genitourinary Tract 291

Benjamin N. Breyer, MD, MAS, FACS

19 Urothelial Carcinoma: Cancers of the Bladder, Ureter, and Renal Pelvis 309

Badrinath R. Konety, MD, MBA; & Peter R. Carroll, MD, MPH

20 Renal Parenchymal Neoplasms 329

Anobel Y. Odisho, MD, MPH; &
Kirsten L. Greene, MD, MS

21 Cancer of the Prostate Gland 351

Matthew R. Cooperberg, MD, MPH;
Samuel L. Washington III, MD; &
Peter R. Carroll, MD, MPH

22 Genital Tumors 377

Sima P. Porten, MD, MPH; &
Joseph C. Presti, Jr., MD

23 Urinary Diversion and Bladder Substitutions 391

Maxwell V. Meng, MD, MPH;
Susan Barbour, RN, MS, WOCN; &
Peter R. Carroll, MD, MPH

24 Systemic Therapy of Urologic Tumors 407

Vadim S. Koshkin, MD; & Eric J. Small, MD

25 Immunotherapy in Urologic Malignancies 415

Arpita Desai, MD; & Eric J. Small, MD

26 Radiotherapy of Urologic Tumors 421

Yun Rose Li, MD, PhD;
Alexander R. Gottschalk, MD, PhD; &
Mack Roach III, MD

27 Neurophysiology and Pharmacology of the Lower Urinary Tract 453

Karl-Erik Andersson, MD, PhD

28 Neurogenic Bladder 473

Anne M. Suskind, MD, MS, FACS

29 Urodynamics 485

Anne M. Suskind, MD, MS, FACS

30 Urinary Incontinence 499

Tom F. Lue, MD, FACS, ScD (Hon); &
Emil A. Tanagho, MD

31 Disorders of the Adrenal Glands 509

Michelle L. McDonald, MD; &
Christopher J. Kane, MD, FACS

32 Disorders of the Kidneys 521

David B. Bayne, MD, MPH;
Jack W. McAninch, MD, FACS, FRCS(E)(Hon); &
Thomas Chi, MD

33 Diagnosis of Medical Renal Diseases 539

Brian K. Lee, MD; & Flavio G. Vincenti, MD

34 Acute Kidney Injury and Oliguria 551

Brian K. Lee, MD; & Flavio G. Vincenti, MD

35 Chronic Kidney Disease and Renal Replacement Therapy 557

Brian K. Lee, MD; &
Flavio G. Vincenti, MD

36 Renal Transplantation 563

John M. Barry, MD

37 Disorders of the Ureter and Ureteropelvic Junction 571

Barry A. Kogan, MD

38 Disorders of the Bladder, Prostate, and Seminal Vesicles 585

Samuel L. Washington III, MD; &
Katsuto Shinohara, MD

39 Male Sexual Dysfunction 605

Amanda B. Reed-Maldonado, MD, FACS; &
Tom F. Lue, MD

40 Women's Sexual Health 631

Alan W. Shindel, MD, MAS; &
Tami S. Rowen, MD, MS

41 Disorders of the Penis and Male Urethra 645

Benjamin N. Breyer, MD, MAS, FACS; &
Jack W. McAninch, MD, FACS, FRCS(E)(Hon)

42 Disorders of the Female Urethra 659

Donna Y. Deng, MD, MS

43 Disorders of Sex Development 671

Laurence S. Baskin, MD

44 Male Infertility 703

Thomas J. Walsh, MD, MS; &
James F. Smith, MD, MS

45 The Aging Male 735

James F. Smith, MD, MS;
Bogdana Schmidt, MD, MPH; &
Thomas J. Walsh, MD, MS

46 Genital Gender-Affirming Surgery: Patient Care, Decision Making, and Surgery Options 747

Maurice M. Garcia, MD, MAS

47 History and Physical Examination in Pediatric Urology 769

Michael DiSandro, MD

48 Introduction to Clinical Research Design 781

June M. Chan, ScD; David Tat, DO; &
Stacey Kenfield, ScD

Index 793

This page intentionally left blank

Contributors

Karl-Erik Andersson, MD, PhD
Institute for Regenerative Medicine
Wake Forest University School of Medicine
Winston Salem, North Carolina

Susan Barbour, RN, MS, WOCN
Palliative Care Services
UCSF School of Medicine
San Francisco, California

John M. Barry, MD
Professor of Urology and Professor of Surgery
Division of Abdominal Organ Transplantation
Organ Health and Science University
Portland, Oregon

Laurence S. Baskin, MD
Chief of Pediatric Urology
University of California Children's Medical Center
UCSF School of Medicine
San Francisco, California
Attending Urologist
Children's Hospital Oakland
Oakland, California

David B. Bayne, MD, MPH
Endourology Fellow
Department of Urology
UCSF School of Medicine
San Francisco, California

Benjamin N. Breyer, MD, MAS, FACS
Associate Professor and Vice Chair
Department of Urology
UCSF School of Medicine
San Francisco, California

Peter R. Carroll, MD, MPH
Professor
Ken and Donna Derr-Chevron Endowed Chair in Prostate Cancer
Department of Urology
UCSF School of Medicine
San Francisco, California

June M. Chan, ScD
Program Director, Genitourinary Cancer Epidemiology and Population Sciences
Department of Urology
UCSF School of Medicine
San Francisco, California

Thomas Chi, MD
Associate Professor and Katzman Endowed Professor in Clinical Urology
Department of Urology
UCSF School of Medicine
San Francisco, California

Matthew R. Cooperberg, MD, MPH
Associate Professor
Department of Urology
Helen Diller Family Comprehensive Cancer Center
UCSF School of Medicine
San Francisco, California

Hillary L. Copp, MD, MS
Associate Professor of Urology and Pediatric Urology Fellowship Director
Benioff Children's Hospital
UCSF School of Medicine
San Francisco, California

Donna Y. Deng, MD, MS
Neurourology Lead, Kaiser Permanente Northern California
Medical Director, Kaiser NorCal Regional Spina Bifida Program
Associate Fellowship Director, Female Pelvic Medicine Reconstructive Surgery, Kaiser East Bay/UCSF
Oakland, California

Arpita Desai, MD
Clinical Instructor
Department of Genitourinary Medical Oncology
Helen Diller Family Comprehensive Cancer Center
UCSF School of Medicine
San Francisco, California

Michael DiSandro, MD
Professor of Urology
Department of Urology
UCSF School of Medicine
San Francisco, California

Daniela Franz, MD
Department of Diagnostic and Interventional Radiology
Klinikum rechts der Isar
Munich Technical University
Munich, Germany

Thomas W. Gaither, MD, MAS
Urology resident
University of California
Los Angeles, California

Maurice M. Garcia, MD, MAS
Associate Professor of Urology and Anatomy (Adjunct)
Departments of Urology and Anatomy
UCSF Medical Center
San Francisco, California
Director, Cedars-Sinai Transgender Surgery and Health Program
Division of Urology
Cedars-Sinai Medical Center
Los Angeles, California

Scott Gerst, MD
Associate Attending Physician
Department of Radiology
Memorial Hospital, Memorial Sloane-Kettering Cancer Center
New York, New York

Rolf Gillitzer, MD
Clinical Director
Department of Urology
Johannes Gutenberg University Medical Center Mainz
Mainz, Germany

Roy L. Gordon, MD
Professor of Interventional Radiology
Department of Radiology
UCSF School of Medicine
San Francisco, California

Alexander R. Gottschalk, MD, PhD
Professor of Radiation Oncology
Director of CyberKnife
Departments of Radiation and Oncology
UCSF School of Medicine
San Francisco, California

Kirsten L. Greene, MD, MS
Professor and Chair
Department of Urology
University of Virginia
Charlottesville, Virginia

Hedvig Hricak, MD, PhD
Chair
Department of Radiology
Memorial Sloan-Kettering Cancer Center
Professor of Radiology
Cornell University
New York, New York

Christopher J. Kane, MD, FACS
Dean of Clinical Affairs
UC San Diego School of Medicine
CEO, UC San Diego Health Physician Group
La Jolla, California

Stacey A. Kenfield, ScD
Associate Professor
Department of Urology
UCSF School of Medicine
San Francisco, California

Barry A. Kogan, MD
Professor, Surgery and Pediatrics
Falk Chair in Urology
Albany Medical College
Albany, New York

Ryan Kohlbrenner, MD
Assistant Professor of Interventional Radiology
Departments of Radiology and Biomedical Imaging
UCSF School of Medicine
San Francisco, California

Badrinath R. Konety, MD, MBA
Associate Dean for Innovation
Professor of Urology
Director of the Institute for Prostate and Urologic Cancers
University of Iowa
Iowa City, Iowa

Vadim S. Koshkin, MD
Assistant Clinical Professor
Genitourinary Medical Oncologist
Departments of Hematology and Oncology
UCSF School of Medicine
San Francisco, California

John N. Krieger, MD
Professor of Urology
University of Washington School of Medicine
Seattle, Washington

Brian K. Lee, MD
Professor of Medicine
The Connie Frank Kidney Transplant Center
UCSF School of Medicine
San Francisco, California

Yun Rose Li, MD, PhD
Resident Physician
Departments of Radiation and Oncology
UCSF School of Medicine
San Francisco, California

Tom F. Lue, MD, FACS, ScD (Hon)
Professor of Urology
Emil Tanagho Endowed Chair in Clinical Urology
Department of Urology
UCSF School of Medicine
San Francisco, California

Kristin Madden, PharmD
Pharmacist
Department of Veterans Affairs
San Antonio, Texas

Jack W. McAninch, MD, FACS, FRCS(E)(Hon)
Professor of Urology
UCSF School of Medicine
San Francisco, California

Michelle L. McDonald, MD
Urologist
San Diego, California

Maxwell V. Meng, MD, MPH
Professor
Department of Urology
UCSF School of Medicine
San Francisco, California

Hiep T. Nguyen, MD
Associate Professor
Surgery and Urology
Harvard Medical School and Children's Hospital
Boston, Massachusetts

Anobel Y. Odisho, MD, MPH
Assistant Professor
Department of Urologic Oncology
UCSF School of Medicine
San Francisco, California

Sima P. Porten, MD, MPH
Assistant professor
Department of Urology
UCSF School of Medicine
San Francisco, California

Joseph C. Presti, Jr., MD
Lead for Urologic Oncology
Kaiser Permanente Northern California
Oakland, California

Amanda B. Reed-Maldonado, MD, FACS
Chief, Male Reproductive Urology
Department of Urology
Tripler Army Medical Center
Honolulu, Hawaii

Mack Roach III, MD
Professor of Radiation Oncology and Urology
Department of Urology
UCSF School of Medicine
San Francisco Comprehensive Cancer Center
San Francisco, California

Tami S. Rowen, MD, MS
Assistant Professor
Departments of Obstetrics, Gynecology, and Reproductive Sciences
UCSF School of Medicine
San Francisco, California

Bogdana Schmidt, MD, MPH
Urologic Oncology Fellow
Stanford University Medical Center
Stanford, California

Alan W. Shindel, MD, MAS
Associate Professor
Department of Urology
University of California
Davis, California

Katsuto Shinohara, MD
Professor
Helen Diller Family Chair in Clinical Urology
Department of Urology
UCSF School of Medicine
San Francisco, California

Eric J. Small, MD
Professor of Medicine and Urology
Urologic Oncology Program and Program Member, Comprehensive Cancer Center
UCSF School of Medicine
San Francisco, California

James F. Smith, MD, MS
Associate Professor
Director, Male Reproductive Health
Departments of Urology, Obstetrics, Gynecology, and Reproductive Sciences
UCSF School of Medicine
San Francisco, California

Marshall L. Stoller, MD
Professor of Urology
Department of Urology
UCSF School of Medicine
San Francisco, California

Anne M. Suskind, MD, MS, FACS
Associate Professor of Urology, Obstetrics, Gynecology, and Reproductive Sciences
Director, Neurourology, Female Pelvic Medicine & Reconstructive Surgery
UCSF School of Medicine
San Francisco, California

Emil A. Tanagho, MD
Professor of Urology
Department of Urology
UCSF School of Medicine
San Francisco, California

David Tat, DO
Infectious Disease Specialist
Moses H. Cone Memorial Hospital
Greensboro, North Carolina

Joachim W. Thüroff, MD
Professor
Department of Urology
University Medical Center
Mannheim, Germany

Flavio G. Vincenti, MD
Professor of Medicine
The Connie Frank Kidney Transplant Center
UCSF School of Medicine
San Francisco, California

Thomas J. Walsh, MD, MS
Associate Professor
Department of Urology
University of Washington School of Medicine
Seattle, Washington

Mary K. Wang, MD
Childrens' Urology
Austin, Texas

Samuel L. Washington, III, MD
Urologic Oncology Clinical Fellow
Department of Urology
UCSF School of Medicine
San Francisco, California

J. Stuart Wolf, Jr., MD, FACS
Professor, Department of Surgery and Perioperative Care
Dell Medical School
The University of Texas at Austin
Austin, Texas

Preface

Smith & Tanagho's General Urology, nineteenth edition, provides the updated information for the understanding, diagnosis, and treatment of urological diseases in a concise and well-organized format. The book is up-to-date, to the point, and readable.

Medical students will find this book useful because of its concise, easy-to-follow format, and its breadth of information on common urological diseases. Residents, as well as practicing physicians in urology, family practice, or general medicine, will find it an efficient and current reference, particularly because of its emphasis on diagnosis and treatment.

This nineteenth edition has been thoroughly updated with clinical information and current references. The reader will find that this edition is written in an uncomplicated, straightforward manner that provides relevant clinical information and guidelines for diagnosis and management of urologic conditions. Chapters on immunotherapy in urologic malignancies, radiotherapy of urologic tumors, urinary incontinence, and vascular interventional radiology have all undergone extensive revision. For this current edition, we have added two chapters on the timely topic of gender dysphoria and introduction to clinical research design.

Many illustrations and figures have been modernized and improved with added color. The classic fine anatomic drawings demonstrate well the important clinical findings.

This book has been one of the leading sources of information for students, trainees, and urologists around the world. In addition to English, this book has been published in many other foreign languages, like Chinese, French, Greek, Italian, Japanese, Korean, Portuguese, Russian, Spanish, and Turkish.

We greatly appreciate the patience and efforts of our McGraw-Hill staff, the expertise of our contributors, and the support of our readers.

Jack W. McAninch, MD, FACS, FRCS(E) (Hon)
Tom F. Lue, MD, FACS, ScD (Hon)
San Francisco, California, January 2020

This page intentionally left blank

1

Anatomy of the Genitourinary Tract

Emil A. Tanagho, MD; & Tom F. Lue, MD, ScD (Hon), FACS

Urology deals with diseases and disorders of the adrenal gland, the male genitourinary tract, and the female urinary tract. These systems are illustrated in Figures 1–1 and 1–2.

ADRENALS

Gross Appearance

A. Anatomy

Each kidney is capped by an adrenal gland, and both organs are enclosed within Gerota's (perirenal) fascia. Each adrenal gland weighs 4–5 g. The right adrenal is triangular in shape; the left is more rounded and crescentic. The average dimensions are 3 cm width, 5 cm length, and 1 cm thickness. Each gland is composed of a cortex, chiefly influenced by the pituitary gland, and a medulla derived from chromaffin tissue (Avisse et al, 2000; O'Donoghue et al, 2010).

B. Relations

Figure 1–2 shows the relationships between the adrenals and other organs. The right adrenal lies between the liver and the vena cava. The left adrenal lies close to the aorta and is covered on its lower surface by the pancreas. The spleen lies superior and lateral to it.

Histology

The adrenal cortex, which makes up 85% of the mass, is composed of three distinct layers: the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. The medulla lies centrally and is made up of polyhedral cells with hormone-containing granular cytoplasm. These chromaffin cells are accompanied by a small number of sympathetic ganglion cells.

Blood Supply

A. Arterial

Each adrenal gland receives three arteries: one from the inferior phrenic artery, one from the aorta, and one from the renal artery.

B. Venous

Blood from the right adrenal gland is drained by a very short vein into the vena cava; the left adrenal vein terminates in the left renal vein.

Lymphatics

The lymphatic vessels accompany the suprarenal vein and drain into the lumbar lymph nodes.

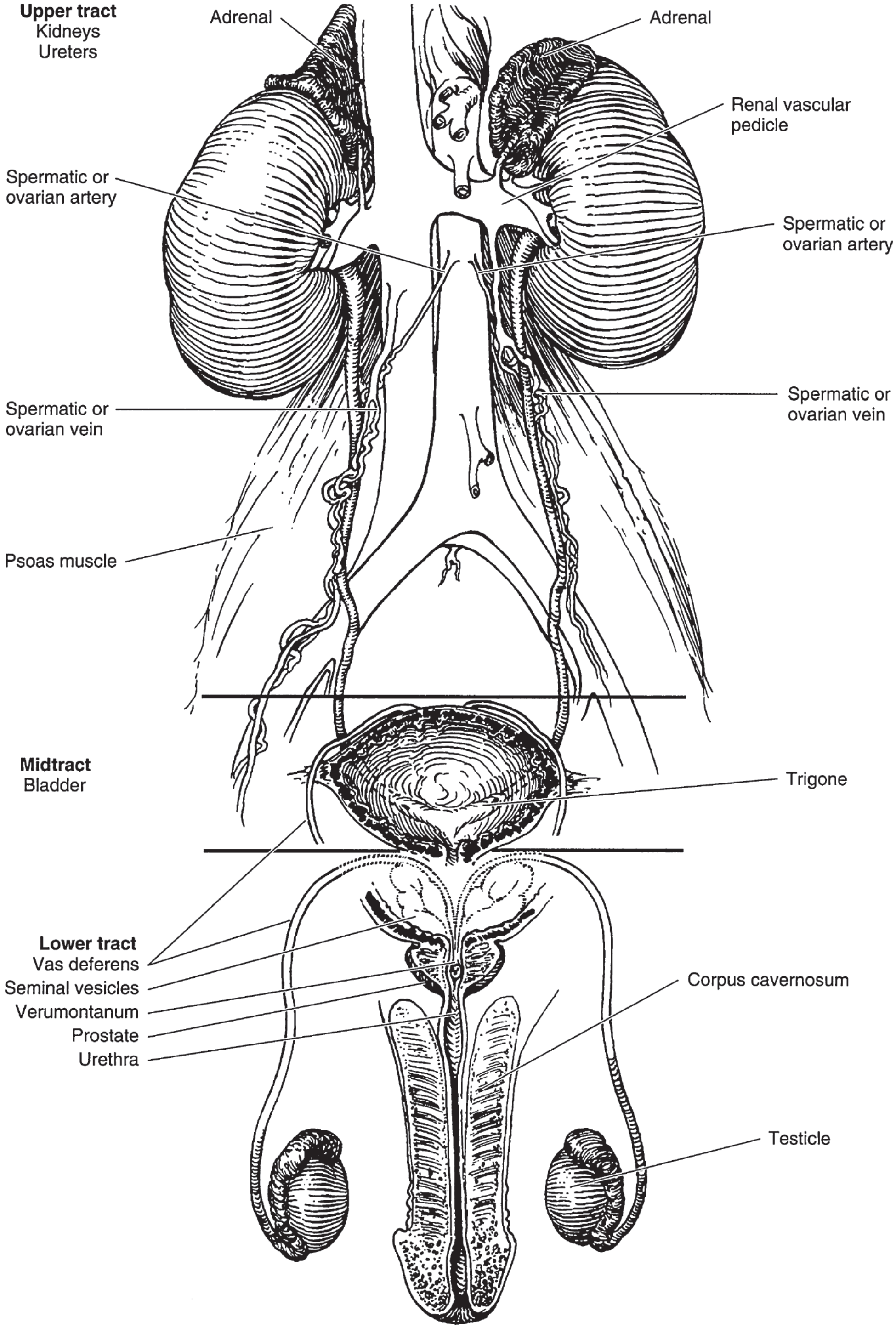
KIDNEYS

Gross Appearance

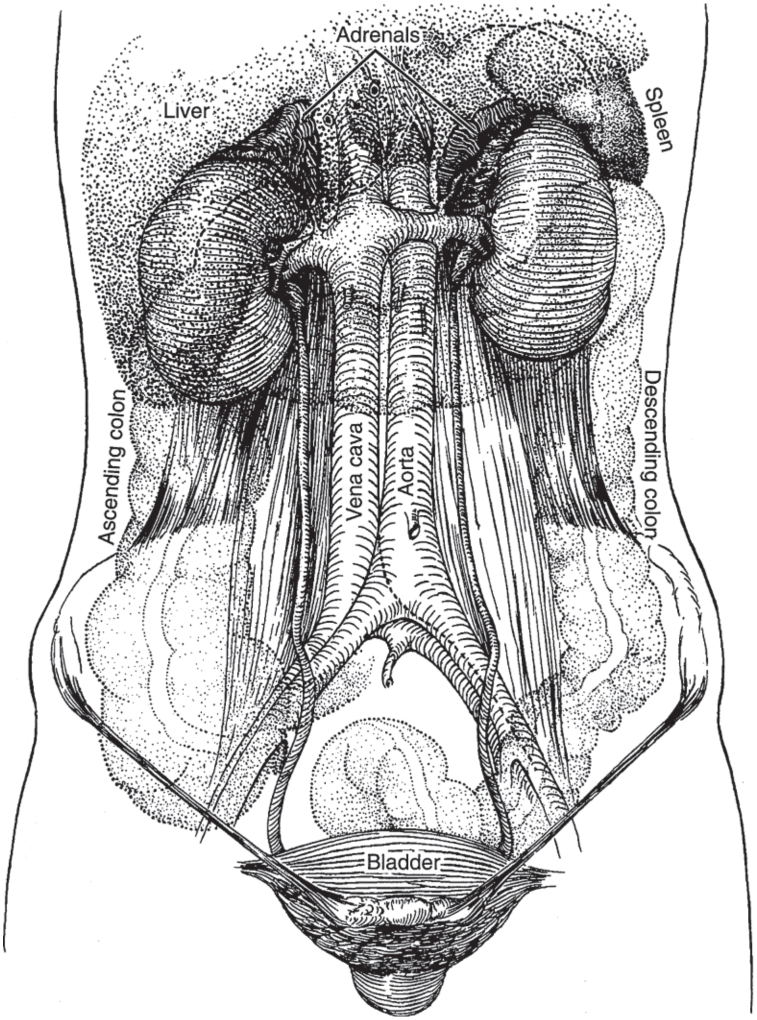
A. Anatomy

The kidneys lie along the borders of the psoas muscles and are therefore obliquely placed. The position of the liver causes the right kidney to be lower than the left (Figures 1–2 and 1–3). The adult kidney weighs between 125 and 170 g in men and 115 and 155 g in women. It is about 10–12 cm long, 5–7 cm wide, and 3–5 cm thick.

The kidneys are supported by the perirenal fat (which is enclosed in the perirenal fascia), the renal vascular pedicle, abdominal muscle tone, and the general bulk of the abdominal viscera (Rusinek et al, 2004). Variations in these factors permit variations in the degree of renal mobility. The average descent on inspiration or on assuming the upright position is 4–5 cm. Lack of mobility suggests abnormal fixation (eg, perinephritis), but extreme mobility is not necessarily pathologic.



▲ **Figure 1–1.** Anatomy of the male genitourinary tract. The upper tract and midtract have urologic function only. The lower tract has both genital and urinary functions.



▲ **Figure 1–2.** Relations between the kidneys, ureters, and bladder (anterior aspect).

On longitudinal section (Figure 1–4), the kidney is seen to be made up of an outer cortex, a central medulla, and the internal calices and pelvis. The cortex is homogeneous in appearance. Portions of it project toward the pelvis between the papillae and fornices and are called the **columns of Bertin**. The medulla consists of numerous pyramids formed by the converging collecting renal tubules, which drain into the minor calices at the tip of the papillae.

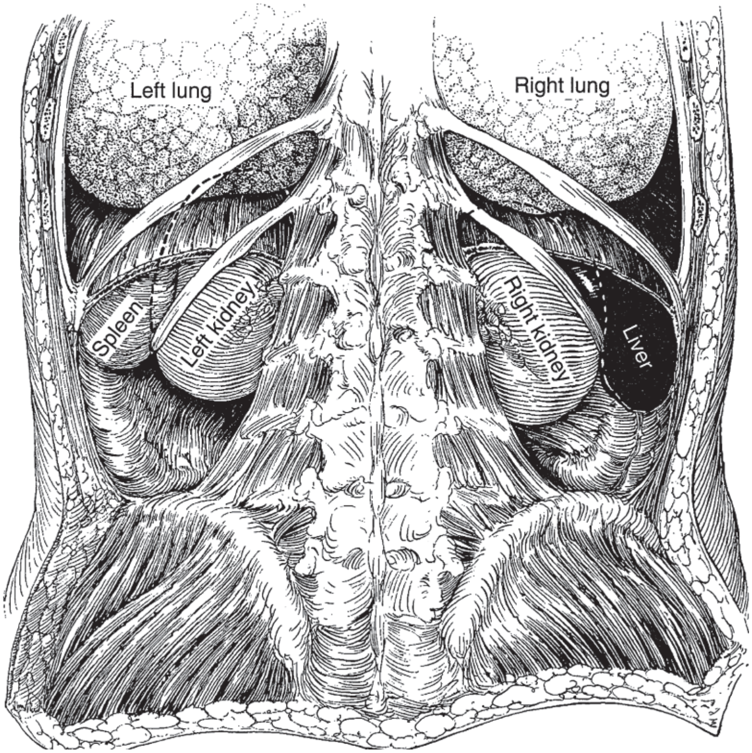
B. Relations

Figures 1–2 and 1–3 show the relationships between the kidneys and adjacent organs and structures. Their intimacy with intraperitoneal organs and the autonomic innervation that they share with these organs explain, in part, some of the gastrointestinal symptoms that accompany kidney diseases (Glassberg, 2002).

Histology

A. Nephron

The functioning unit of the kidney is the nephron, which is composed of a tubule that has both secretory and excretory functions (Figure 1–4). The secretory portion is contained largely within the cortex and consists of a renal corpuscle and the secretory part of the renal tubule. The excretory portion of this duct lies in the medulla. The renal corpuscle is composed of the vascular glomerulus, which projects into Bowman's capsule, which, in turn, is continuous with the epithelium of the proximal convoluted tubule. The secretory portion of the renal



▲ **Figure 1–3.** Relations between the kidneys (posterior aspect). The dashed lines represent the outline of the kidneys, where they are obscured by overlying structures.

tubule is made up of the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule.

The excretory portion of the nephron is the collecting tubule, which is continuous with the distal end of the ascending limb of the convoluted tubule. It empties its contents through the tip (papilla) of a pyramid into a minor calyx.

B. Supporting Tissue

The renal stroma is composed of loose connective tissue and contains blood vessels, capillaries, nerves, and lymphatics.

▶ Blood Supply (Figures 1–2, 1–4, and 1–5)

A. Arterial

Usually there is one renal artery, a branch of the aorta that enters the hilum of the kidney between the pelvis, which normally lies posteriorly, and the renal vein. It may branch before it reaches the kidney, and two or more separate arteries may be noted (Budhiraja et al, 2010). In duplication of the pelvis and ureter, it is common for each renal segment to have its own arterial supply.

The renal artery divides into anterior and posterior branches. The posterior branch supplies the midsegment of the posterior surface. The anterior branch supplies both upper and lower poles as well as the entire anterior surface. The renal arteries are all end arteries.

The renal artery branches further divide into interlobar arteries, which travel in the columns of Bertin (between the pyramids) and then arch along the base of the pyramids (arcuate arteries). These arteries then divide as interlobular arteries. From these vessels, smaller (afferent) branches pass to the glomeruli. From the glomerular tuft, efferent arterioles pass to the tubules in the stroma.

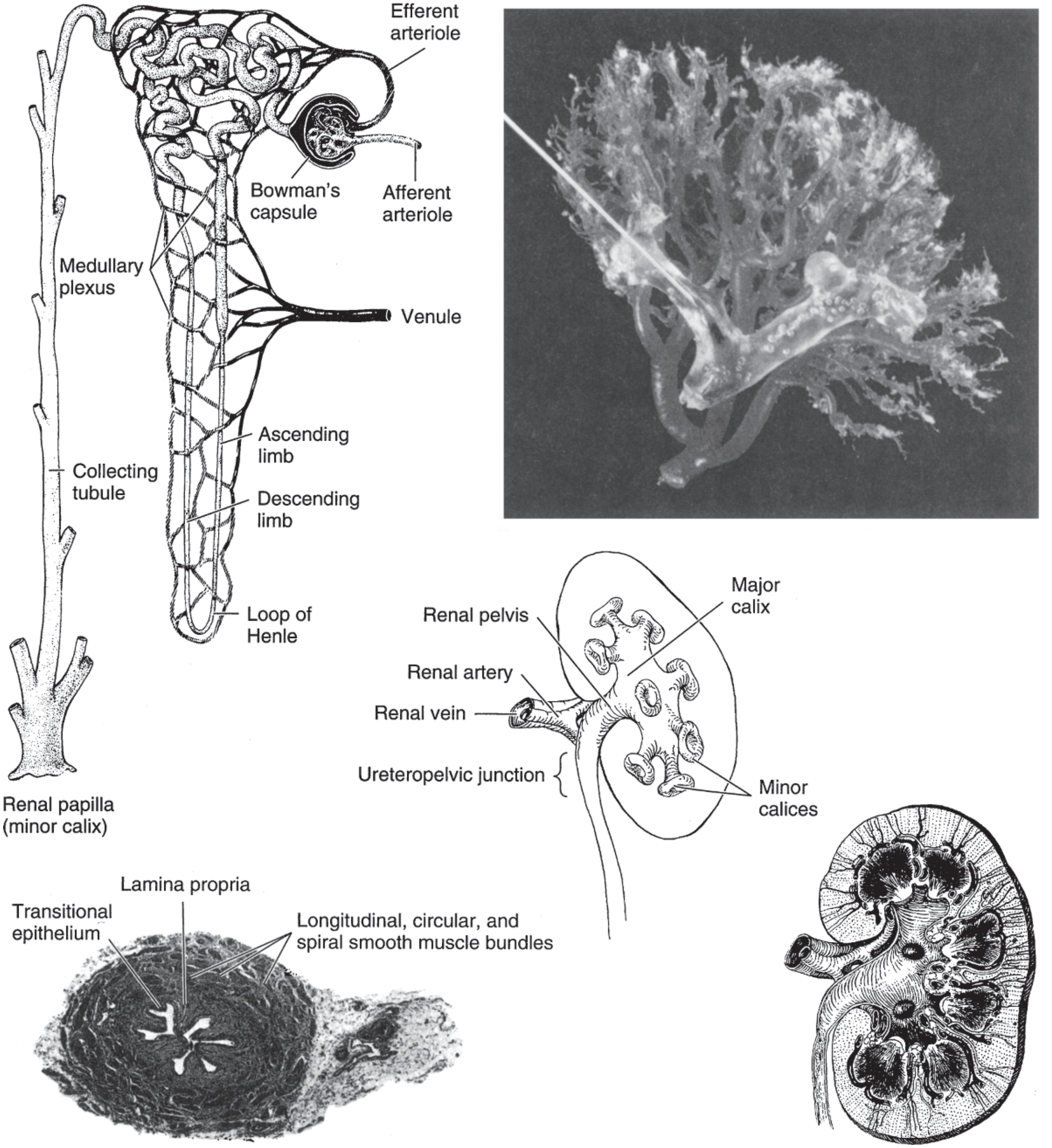
B. Venous

The renal veins are paired with the arteries, but any of them will drain the entire kidney if the others are tied off.

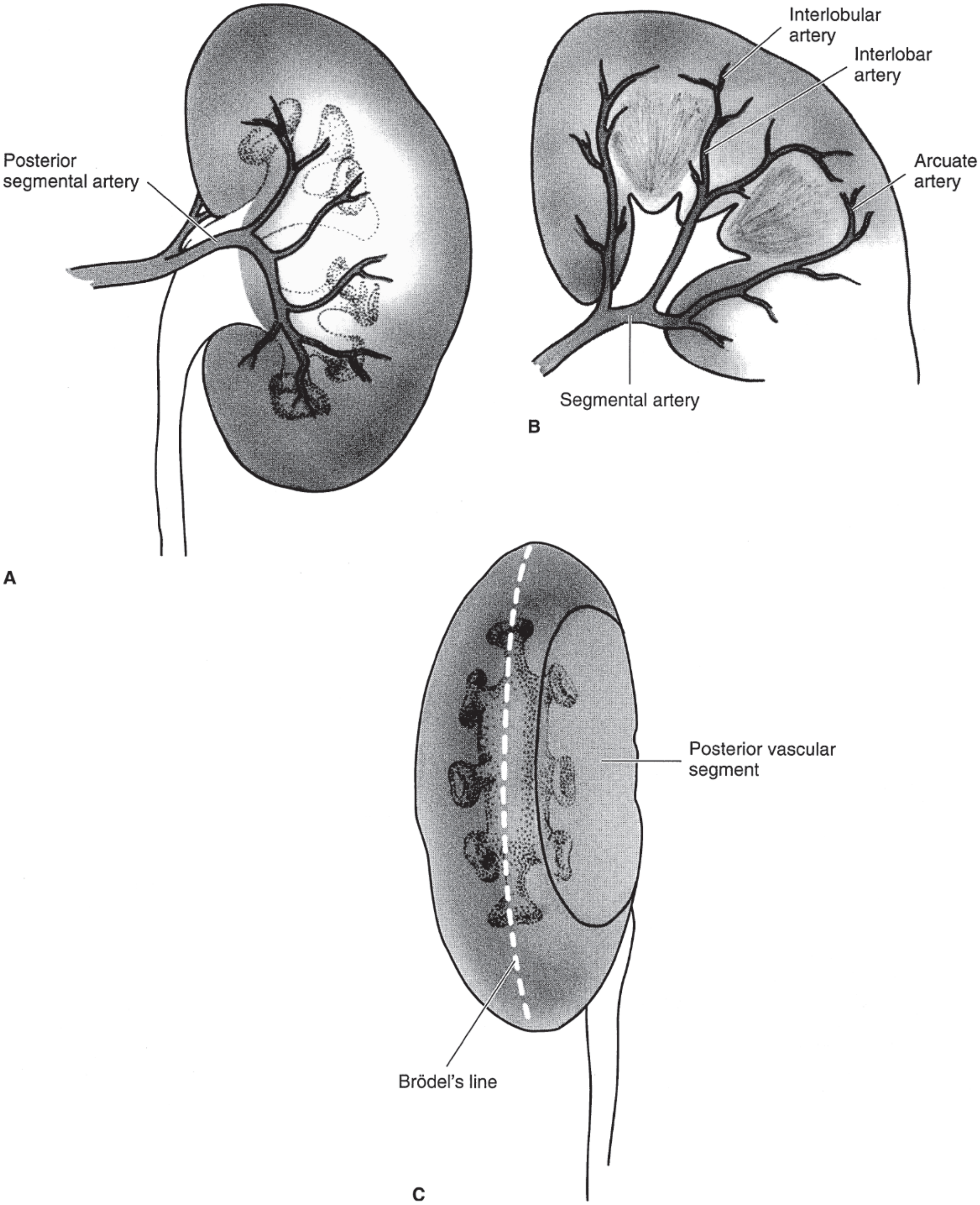
Although the renal artery and vein are usually the sole blood vessels of the kidney, accessory renal vessels are common and may be of clinical importance if they are so placed so as to compress the ureter, in which case hydronephrosis may result.

▶ Nerve Supply

The renal nerves derived from the renal plexus accompany the renal vessels throughout the renal parenchyma.



▲ **Figure 1–4.** Anatomy and histology of the kidney and ureter. ***Upper left:*** Diagram of the nephron and its blood supply. (Courtesy of Merck, Sharp, Dohme: Seminar. 1947; 9[3].) ***Upper right:*** Cast of the pelvic caliceal system and the arterial supply of the kidney. ***Middle:*** Renal calices, pelvis, and ureter (posterior aspect). ***Lower left:*** Histology of the ureter. The smooth-muscle bundles are arranged in both spirally and longitudinally. ***Lower right:*** Longitudinal section of kidney showing calices, pelvis, ureter, and renal blood supply (posterior aspect).



▲ **Figure 1–5.** *(**A**)* The posterior branch of the renal artery and its distribution to the central segment of the posterior surface of the kidney. *(**B**)* Branches of the anterior division of the renal artery supplying the entire anterior surface of the kidney as well as the upper and lower poles at both surfaces. The segmental branches lead to interlobar, arcuate, and interlobular arteries. *(**C**)* The lateral convex margin of the kidney. Brödel's line, which is 1 cm from the convex margin, is the bloodless plane demarcated by the distribution of the posterior branch of the renal artery.

Lymphatics

The lymphatics of the kidney drain into the lumbar lymph nodes.

CALICES, RENAL PELVIS, AND URETER

Gross Appearance

A. Anatomy

1. Calices—The tips of the minor calices (8–12 in number) are indented by the projecting pyramids (Figure 1–4). These calices unite to form two or three major calices that join to form the renal pelvis (Sozen et al, 2008).

2. Renal pelvis—The pelvis may be entirely intrarenal or partly intrarenal and partly extrarenal. Inferomedially, it tapers to join the ureter.

3. Ureter—The adult ureter is about 30 cm long, varying in direct relation to the height of the individual. It follows a rather smooth S curve. Areas that stones are often impacted are (a) at the ureteropelvic junction, (b) where the ureter crosses over the iliac vessels, and (c) where it courses through the bladder wall.

B. Relations

1. Calices—The calices are intrarenal and are intimately related to the renal parenchyma.

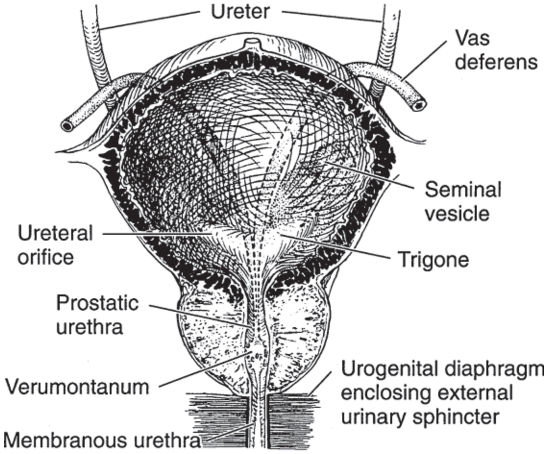
2. Renal pelvis—If the pelvis is partly extrarenal, it lies along the lateral border of the psoas muscle and on the quadratus lumborum muscle; the renal vascular pedicle is just anterior to it. The left renal pelvis lies at the level of the first or second lumbar vertebra; the right pelvis is a little lower.

3. Ureter—On their course downward, the ureters lie on the psoas muscles, pass medially to the sacroiliac joints, and then swing laterally near the ischial spines before passing medially to enter the base of the bladder (Figure 1–2). In females, the uterine arteries are closely related to the juxtavesical portion of the ureters. The ureters are covered by the posterior peritoneum; their lowermost portions are closely attached to it, while the juxtavesical portions are embedded in vascular retroperitoneal fat (Koff, 2008).

The vasa deferentia, as they leave the internal inguinal rings, sweep over the lateral pelvic walls anterior to the ureters (Figure 1–6). They lie medial to the latter before joining the seminal vesicle and penetrating the base of the prostate to become the ejaculatory ducts.

Histology (Figure 1–4)

The walls of the calices, pelvis, and ureters are composed of transitional cell epithelium under which lies loose connective tissue (lamina propria). External to these are a mixture of helical and longitudinal smooth-muscle fibers. They are not arranged in discrete layers. The outermost adventitial coat is composed of fibrous connective tissue.



▲ **Figure 1–6.** Anatomy and relations between the ureters, bladder, prostate, seminal vesicles, and vasa deferentia (anterior view).

Blood Supply

A. Arterial

The renal calices, pelvis, and upper ureters derive their blood supply from the renal arteries; the midureter is fed by the internal spermatic (or ovarian) arteries. The lowermost portion of the ureter is served by branches from the common iliac, internal iliac (hypogastric), and vesical arteries.

B. Venous

The veins of the renal calices, pelvis, and ureters are paired with the arteries.

Lymphatics

The lymphatics of the upper portions of the ureters as well as those from the pelvis and calices enter the lumbar lymph nodes. The lymphatics of the midureter pass to the internal iliac (hypogastric) and common iliac lymph nodes; the lower ureteral lymphatics empty into the vesical and hypogastric lymph nodes.

BLADDER

Gross Appearance

The bladder is a hollow muscular organ that serves as a reservoir for urine. In women, its posterior wall and dome are invaginated by the uterus. The adult bladder normally has a capacity of 400–500 mL. The wall of the bladder is about 3–5 mm in thickness; it is thinner when it is distended.

A. Anatomy

When empty, the adult bladder lies behind the pubic symphysis and is largely a pelvic organ. In infants and children, it is situated higher (Berrocal et al, 2002). When it is full, it rises well above the symphysis and can readily be palpated or percussed. When overdistended, as in acute or chronic urinary retention, it may cause the lower abdomen to bulge visibly.

Extending from the dome of the bladder to the umbilicus is a fibrous cord, the median umbilical ligament, which represents the obliterated urachus. The ureters enter the bladder posteroinferiorly in an oblique manner and at these points are about 5 cm apart (Figure 1–6). The orifices, situated at the extremities of the crescent-shaped interureteric ridge that forms the proximal border of the trigone, are about 2.5 cm apart. The trigone occupies the area between the ridge and the bladder neck.

The internal sphincter, or bladder neck, is not a true circular sphincter but a thickening formed by interlaced and converging muscle fibers of the detrusor as they pass distally to become the smooth muscle component of the urethra.

B. Relations

In males, the bladder is related posteriorly to the seminal vesicles, vasa deferentia, ureters, and rectum (Figures 1–7 and 1–8). In females, the uterus and vagina are interposed between the bladder and rectum (Figure 1–9). The dome and posterior surfaces are covered by peritoneum; hence, in this area, the bladder is closely related to the small intestine and sigmoid colon. In both males and females, the bladder is related to the posterior surface of the pubic symphysis, and, when distended, it is in contact with the lower abdominal wall.

Histology (Figure 1–10)

The mucosa of the bladder is composed of transitional epithelium. Beneath it is a well-developed submucosal layer formed largely of connective and elastic tissues. The mucosa may be considered as a single functional unit that consists of the epithelial layer, basement membrane, and lamina propria. Physical or chemical stress on the bladder elicits releases of multiple factors that modulate afferent and efferent nerve activities (Fry and Vahabi, 2016). External to the submucosa is the detrusor muscle that is made up of a mixture of smooth-muscle fibers arranged at random in a longitudinal, circular, and spiral manner without any layer formation or specific orientation except for proximity to the internal meatus, where the detrusor muscle assumes three definite layers: inner longitudinal, middle circular, and outer longitudinal (John et al, 2001).

Blood Supply

A. Arterial

The bladder is supplied by the superior, middle, and inferior vesical arteries, which arise from the anterior trunk of the internal iliac (hypogastric) artery, and by smaller branches from the obturator and inferior gluteal arteries. In females, the uterine and vaginal arteries also send branches to the bladder.

B. Venous

Surrounding the bladder is a rich plexus of veins that ultimately empties into the internal iliac (hypogastric) veins.

Nerve Supply

The bladder receives innervation from sympathetic and parasympathetic nervous systems. The sensory afferent of the bladder originates from both subepithelial nerve endings and nerve fibers between detrusor muscle bundles (Andersson, 2010; Birder et al, 2010; McCloskey, 2010).

Lymphatics

The lymphatics of the bladder drain into the vesical, external iliac, internal iliac (hypogastric), and common iliac lymph nodes.

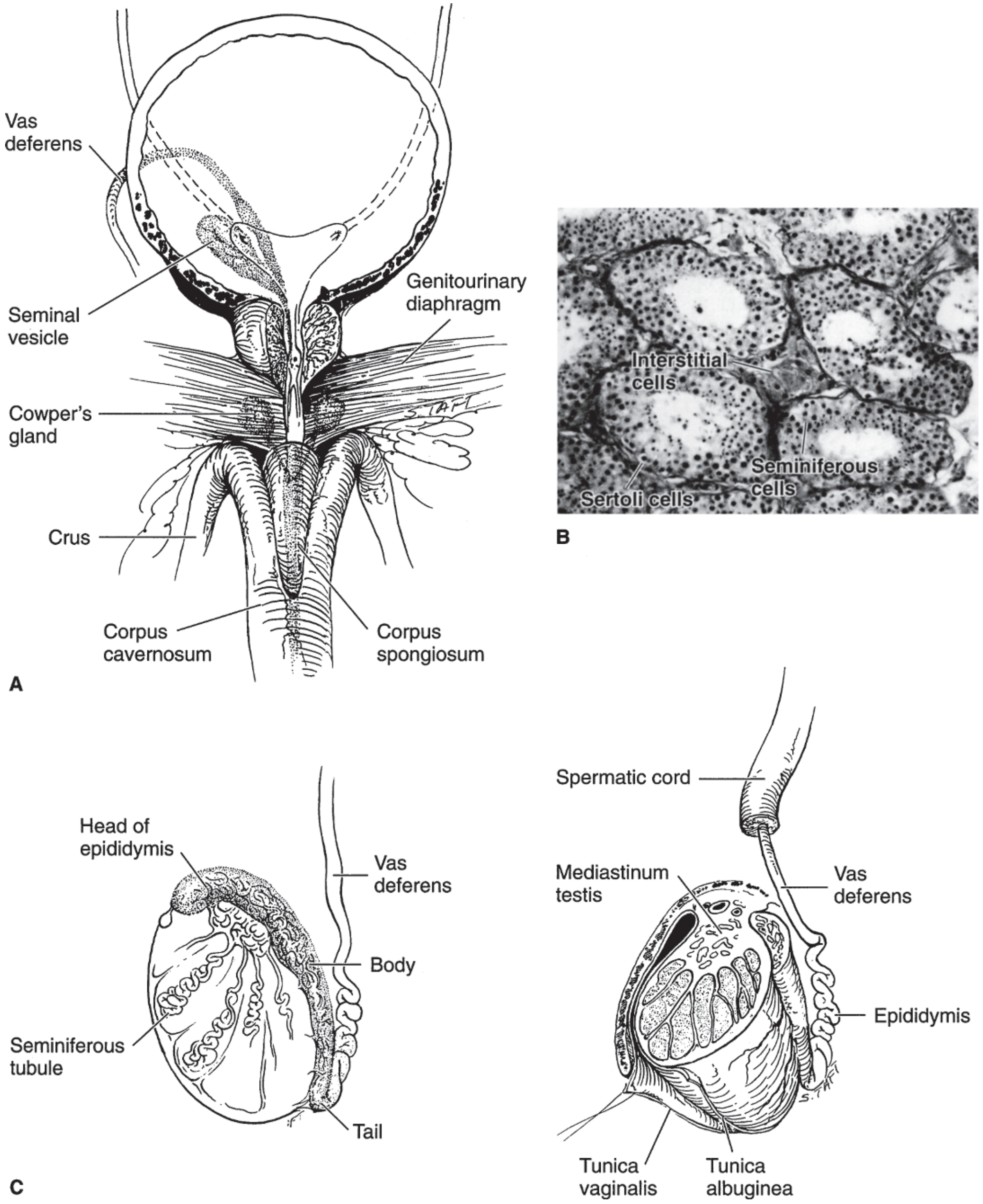
PROSTATE GLAND

Gross Appearance

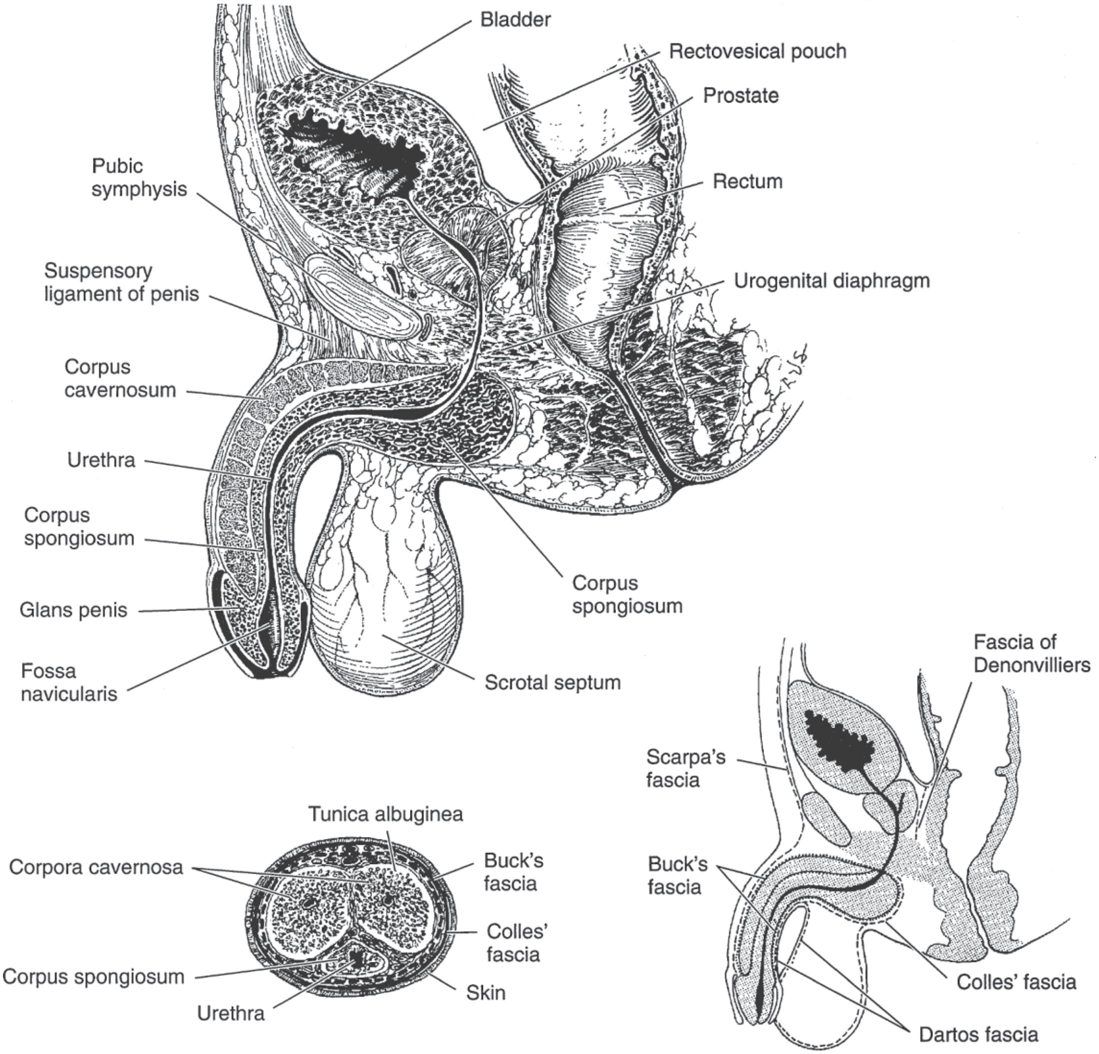
A. Anatomy

The prostate is a fibromuscular and glandular organ lying just inferior to the bladder (Figures 1–6 and 1–7). The normal prostate weighs about 20 g and contains the posterior urethra, which is about 2.5 cm in length. It is supported anteriorly by the puboprostatic ligaments and inferiorly by the urogenital diaphragm (Figure 1–6). The prostate is perforated posteriorly by the ejaculatory ducts, which pass obliquely to empty through the verumontanum on the floor of the prostatic urethra just proximal to the striated external urinary sphincter (Figure 1–11).

The prostate can be subdivided into two ways: by lobe or by zone. The lobe classification is often used in cystourethroscopic examinations and consists of five lobes: anterior, posterior, median, right lateral, and left lateral. The zone classification is often used in pathology. McNeal (1981) divides the prostate into four zones: peripheral zone, central zone (surrounds the ejaculatory ducts), transitional zone (surrounds the urethra), and anterior fibromuscular zone (Myers et al, 2010) (Figure 1–12). The segment of urethra that traverses the prostate gland is the prostatic urethra. It is lined by an inner longitudinal layer of muscle (continuous with a similar layer of the vesical wall). Incorporated within the



▲ Figure 1–7. *(**A**)* Anatomic relationship between the bladder, prostate, prostatomembranous urethra, and root of the penis. *(**B**)* Histology of the testis. Seminiferous tubules lined by supporting basement membrane for the Sertoli and spermatogenic cells. The latter are in various stages of development. *(**C**)* Cross sections of the testis and epididymis. (Images [A] and [C] reproduced with permission from Walsh PC, Campbell MF: Campbell's Urology, 6th ed. Philadelphia, PA: Saunders; 1992.)



▲ **Figure 1–8.** ***Top:*** Relations between the bladder, prostate, seminal vesicles, penis, urethra, and scrotal contents. ***Lower left:*** Transverse section through the penis. The paired upper structures are the corpora cavernosa. The single lower body surrounding the urethra is the corpus spongiosum. ***Lower right:*** Fascial planes of the lower genitourinary tract. (After Wesson.)

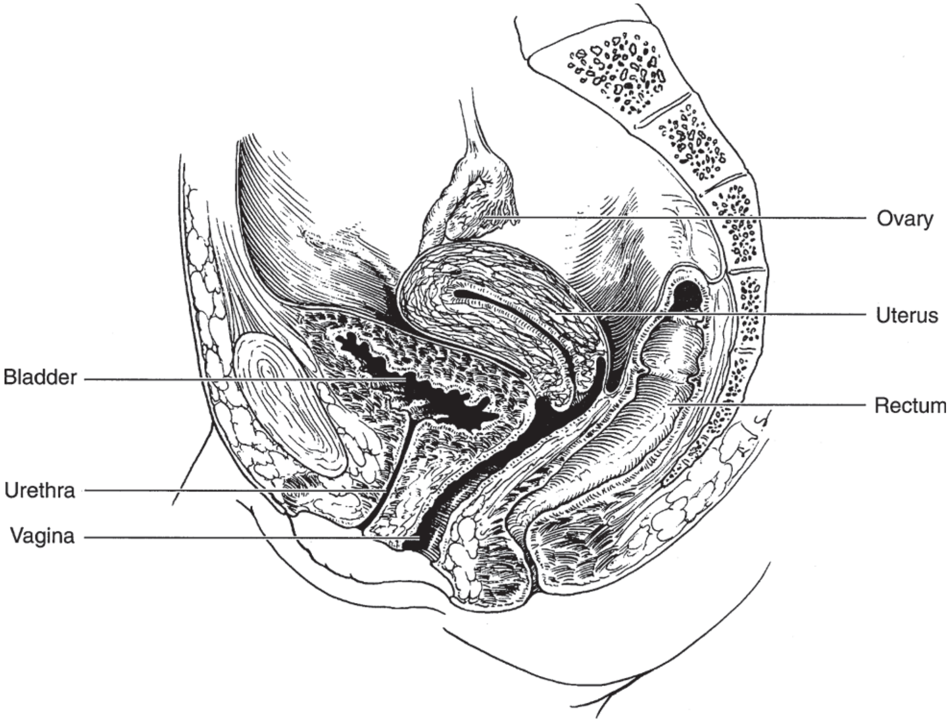
prostate gland is an abundant amount of smooth musculature derived primarily from the external longitudinal bladder musculature. This musculature represents the involuntary smooth muscle sphincter of the posterior urethra in males.

B. Relations

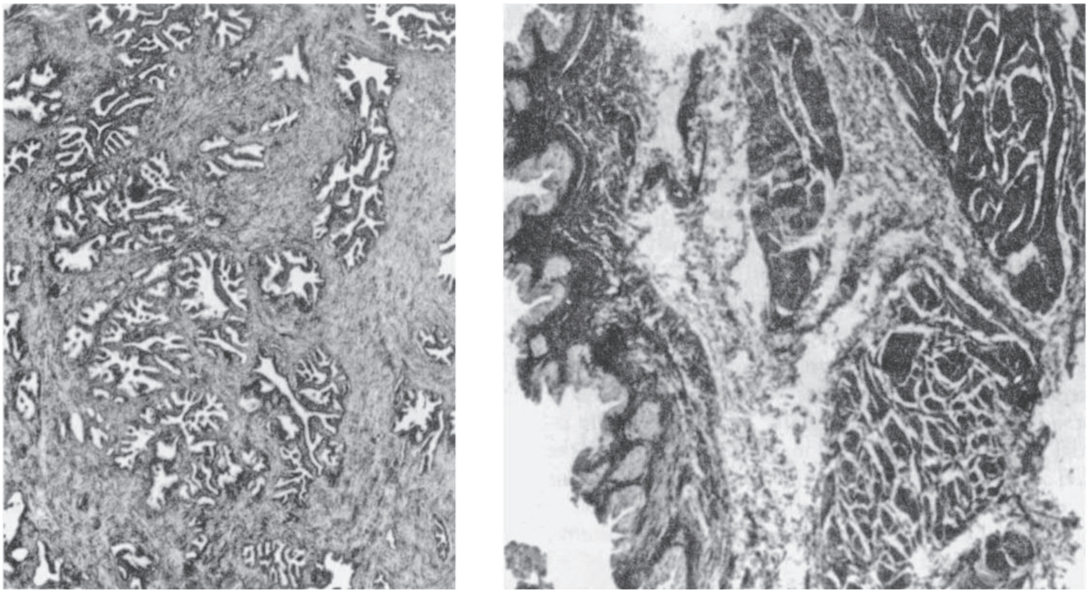
The prostate gland lies behind the pubic symphysis. Located closely to the posterosuperior surface are the vasa deferentia and seminal vesicles (Figure 1–7). Posteriorly, the prostate is separated from the rectum by the two layers of Denonvilliers' fascia, serosal rudiments of the pouch of Douglas, which once extended to the urogenital diaphragm (Raychaudhuri and Cahill, 2008) (Figure 1–8).

▶ Histology (Figure 1–10)

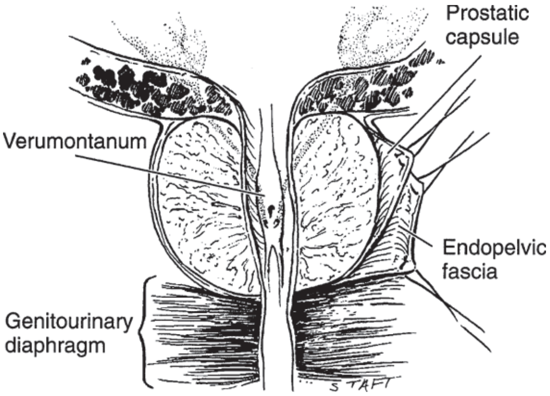
The prostate consists of a thin fibrous capsule under which lie circularly oriented smooth-muscle fibers and collagenous tissue that surrounds the urethra (involuntary



▲ **Figure 1–9.** Anatomy and relations of the bladder, urethra, uterus and ovary, vagina, and rectum.



▲ **Figure 1–10.** ***Left:*** Histology of the prostate. Epithelial glands embedded in a mixture of connective and elastic tissue and smooth muscle. ***Right:*** Histology of the bladder. The mucosa is transitional cell in type and lies on a well-developed submucosal layer of connective tissue. The detrusor muscle is composed of interlacing longitudinal, circular, and spiral smooth-muscle bundles.



▲ **Figure 1–11.** Section of the prostate gland shows the prostatic urethra, verumontanum, and crista urethralis, in addition to the opening of the prostatic utricle and the two ejaculatory ducts in the midline. Note that the prostate is surrounded by the prostatic capsule, which is covered by another prostatic sheath derived from the endopelvic fascia. The prostate is resting on the genitourinary diaphragm. (Reproduced with permission from Walsh PC, Campbell MF: Campbell's Urology, 6th ed. Philadelphia, PA: Saunders; 1992.)

sphincter). Deep in this layer lies the prostatic stroma, composed of connective tissues and smooth-muscle fibers in which are embedded the epithelial glands. These glands drain into the major excretory ducts (about 25 in number), which open chiefly on the floor of the urethra between the verumontanum and the vesical neck. Just beneath the transitional epithelium of the prostatic urethra lie the periurethral glands.

Blood Supply

A. Arterial

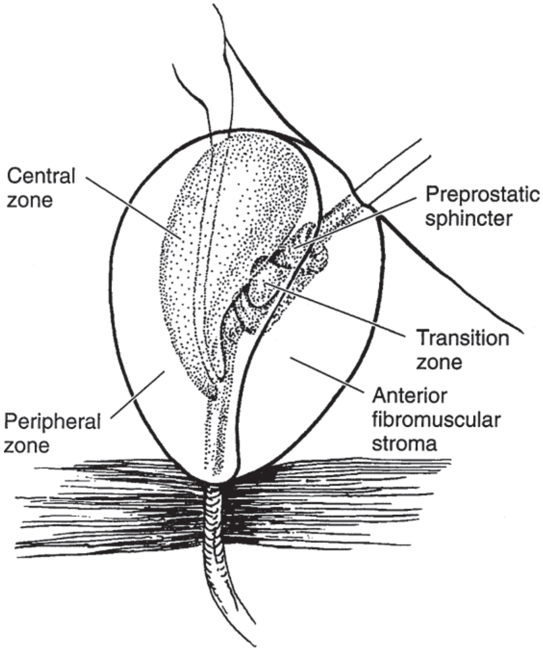
The arterial supply to the prostate is derived from the inferior vesical, internal pudendal, and middle rectal (hemorrhoidal) arteries.

B. Venous

The veins from the prostate drain into the periprostatic plexus, which has connections with the deep dorsal vein of the penis and the internal iliac (hypogastric) veins.

Nerve Supply

The prostate gland receives a rich innervation from the sympathetic and parasympathetic nerves of the inferior hypogastric plexus.



▲ **Figure 1–12.** Anatomy of the prostate gland. Prostatic adenoma develops from the periurethral glands at the site of the median or lateral lobes. The posterior lobe, however, is prone to cancerous degeneration. (Adapted with permission from McNeal JE: The zonal anatomy of the prostate. Prostate 1981;2(1):35–49.)

Lymphatics

The lymphatics from the prostate drain into the internal iliac (hypogastric), sacral, vesical, and external iliac lymph nodes (Saokar et al, 2010).

SEMINAL VESICLES

Gross Appearance

The seminal vesicles lie just cephalic to the prostate under the base of the bladder (Figures 1–6 and 1–7). They are about 6 cm long and quite soft. Each vesicle joins its corresponding vas deferens to form the ejaculatory duct (Kim et al, 2009). The ureters lie medial to each, and the rectum is contiguous with their posterior surfaces.

Histology

The mucous membrane is pseudostratified. The submucosa consists of dense connective tissue covered by a thin layer of muscle that, in turn, is encapsulated by connective tissue.

Blood Supply

The blood supply of the seminal vesicles is similar to that of the prostate gland.

Nerve Supply

The nerve supply is mainly from the sympathetic nerve plexus.

Lymphatics

The lymphatics of the seminal vesicles are those that serve the prostate.

SPERMATIC CORD

Gross Appearance

The two spermatic cords extend from the internal inguinal rings through the inguinal canals to the testicles (Figure 1–7). Each cord contains the vas deferens, the internal and external spermatic arteries, the artery of the vas, the venous pampiniform plexus (which forms the spermatic vein superiorly), lymph vessels, and nerves (Jen et al, 1999). The entire cord contents are enclosed in investing layers of thin fascia. A few fibers of the cremaster muscle insert on the cords in the inguinal canal (Bhosale et al, 2008; Kim et al, 2009).

Histology

The fascia covering the cord is formed of loose connective tissue that supports arteries, veins, nerve, and lymphatics. The vas deferens is a small, thick-walled tube consisting of an internal mucosa and submucosa surrounded by three well-defined layers of smooth muscle encased in a covering of fibrous tissue. Above the testes, this tube is straight. Its proximal 4 cm tends to be convoluted.

Blood Supply

A. Arterial

The external spermatic artery, a branch of the inferior epigastric, supplies the fascial coverings of the cord. The internal spermatic artery passes through the cord on its way to the testis. The deferential artery is close to the vas.

B. Venous

The veins from the testis and the coverings of the spermatic cord form the pampiniform plexus, which, at the internal inguinal ring, unites to form the spermatic vein.

Lymphatics

The lymphatics from the spermatic cord empty into the external iliac lymph nodes.

EPIDIDYMIS

Gross Appearance

A. Anatomy

The upper portion of the epididymis (globus major) is connected to the testis by numerous efferent ducts from the testis (Figure 1–7). The epididymis consists of a markedly coiled duct that, at its lower pole (globus minor), is continuous with the vas deferens. An appendix of the epididymis is often seen on its upper pole; this is a cystic body that in some cases is pedunculated, but in others, it is sessile.

B. Relations

The epididymis lies posterolateral to the testis and is nearest to the testis at its upper pole. Its lower pole is connected to the testis by fibrous tissue. The vas lies posteromedial to the epididymis.

Histology

The epididymis is covered by serosa. The ductus epididymidis is lined by pseudostratified columnar epithelium throughout its length.

Blood Supply

A. Arterial

The arterial supply to the epididymis comes from the internal spermatic artery and the artery of the vas (deferential artery).

B. Venous

The venous blood drains into the pampiniform plexus, which becomes the spermatic vein.

Lymphatics

The lymphatics drain into the external iliac and internal iliac (hypogastric) lymph nodes.

TESTIS

Gross Appearance

A. Anatomy

The average testicle measures about 4 × 3 × 2.5 cm (Figure 1–7). The volume can be measured by an orchidometer or by a formula with ultrasonic measurement (length × width × height × 0.71). The average volume is 18 mL (ranging from 12 to 30 mL). The testicle has a dense fascial covering called the **tunica albuginea testis**, which, posteriorly, is invaginated somewhat into the body of the testis to form the mediastinum testis. This fibrous mediastinum sends fibrous septa into the testis, thus separating it into about 250 lobules.

The testis is covered anteriorly and laterally by the visceral layer of the serous tunica vaginalis, which is continuous with the parietal layer that separates the testis from the scrotal wall (Bidarkar and Hutson, 2005). A small amount of fluid normally exists within the tunica vaginalis sac. At the upper pole of the testis is the appendix testis, a small pedunculated or sessile body similar in appearance to the appendix of the epididymis.

B. Relations

The testis is closely attached posterolaterally to the epididymis, particularly at its upper and lower poles (Klonisch et al, 2004).

Histology (Figure 1–7)

Each lobule contains one to four markedly convoluted seminiferous tubules, each of which is about 60 cm long. These ducts converge at the mediastinum testis, where they connect with the efferent ducts that drain into the epididymis.

The seminiferous tubule has a basement membrane containing connective and elastic tissue. This supports the seminiferous cells that are of two types: (1) Sertoli (supporting) cells and (2) spermatogenic cells. The stroma between the seminiferous tubules contains connective tissue in which the interstitial Leydig cells are located.

Blood Supply

The blood supply to the testes is closely associated with that to the kidneys because of the common embryologic origin of the two organs.

A. Arterial

The arteries to the testes (internal spermatics) arise from the aorta just below the renal arteries and course through the spermatic cords to the testes, where they anastomose with the arteries of the vasa deferentia that branch off from the internal iliac (hypogastric) artery.

B. Venous

The blood from the testis returns in the pampiniform plexus of the spermatic cord. At the internal inguinal ring, the pampiniform plexus forms the spermatic vein.

The right spermatic vein enters the vena cava just below the right renal vein; the left spermatic vein empties into the left renal vein.

Lymphatics

The lymphatic vessels from the testes pass to the lumbar lymph nodes, which, in turn, are connected to the mediastinal nodes.

SCROTUM

Gross Appearance

Beneath the corrugated skin of the scrotum lies the dartos muscle. Deep to this are the three fascial layers derived from the abdominal wall at the time of testicular descent. Beneath these is the parietal layer of the tunica vaginalis (Kim et al, 2007).

The scrotum is divided into two sacs by a septum of connective tissue. The scrotum not only supports the testes but also, by relaxation or contraction of its muscular layer, helps to regulate their temperature.

Histology

The dartos muscle, under the skin of the scrotum, is nonstriated. The deeper layer is made up of connective tissue.

Blood Supply

A. Arterial

The arteries to the scrotum arise from the femoral, internal pudendal, and inferior epigastric arteries.

B. Venous

The veins are paired with the arteries.

Lymphatics

The lymphatics drain into the superficial inguinal and subinguinal lymph nodes.

PENIS AND MALE URETHRA

Gross Appearance

The penis is composed of two corpora cavernosa and the corpus spongiosum, which contains the urethra. The corpus spongiosum enlarges distally and forms the glans penis. Each corpus is enclosed in a fascial sheath (tunica albuginea), and all three corpora are surrounded by a thick fibrous envelope known as *Buck's fascia*. A covering of skin, devoid of fat, is loosely wrapped these bodies. The prepuce forms a hood over the glans.

Beneath the skin of the penis (and scrotum) and extending from the base of the glans to the urogenital diaphragm is Colles' fascia, which is continuous with Scarpa's fascia of the lower abdominal wall (Figure 1–8).

The proximal ends of the corpora cavernosa are attached to the pelvic bones just anterior to the ischial tuberosities. The ischiocavernosus muscles insert into the lateral surface of the tunica albuginea at the proximal corpora cavernosa. Occupying a depression of their ventral surface in the midline is the corpus spongiosum, which is connected proximally to the undersurface of the urogenital diaphragm, below which lies the urethral bulb. This portion of the corpus spongiosum is surrounded by the bulbospongiosus muscle.

The suspensory ligament of the penis arises from the linea alba and pubic symphysis and inserts into the fascial covering of the corpora cavernosa.

Histology

A. Corpora and Glans Penis

The corpora cavernosa, the corpus spongiosum, and the glans penis are composed of smooth muscles, intracavernosal struts (corpus cavernosum only), and endothelium-lined sinusoids. The sympathetic and parasympathetic (as well as the nonadrenergic, noncholinergic [NANC]) nerve terminals are often seen around the vessels and near the smooth muscles.

B. Urethra

The urethral mucosa that traverses the glans penis is formed of squamous epithelium. Proximal to this, the mucosa is transitional in type. Underneath the mucosa is the submucosa that contains connective and elastic tissue and smooth muscle. In the submucosa are the numerous glands of Littre, whose ducts connect with the urethral lumen. The urethra is surrounded by the vascular corpus spongiosum and the glans penis.

Blood Supply

A. Arterial

The penis and urethra are supplied by the internal pudendal arteries. Each artery divides into a cavernous artery of the penis (which supplies the corpora cavernosa), a dorsal artery of the penis, and the bulbourethral artery. These branches supply the corpus spongiosum, the glans penis, and the urethra. Accessory pudendal arteries originate from inferior vesical, obturator, or other arteries may also supply the penis (Henry et al, 2017).

B. Venous

The superficial dorsal vein lies external to Buck's fascia and drains to the saphenous vein. The deep dorsal vein is placed beneath Buck's fascia and lies between the dorsal arteries. The cavernous veins drain the hilum and crura of the penis. These veins connect with the pudendal plexus that drains into the internal pudendal vein and periprostatic plexus.

Lymphatics

Lymphatic drainage from the skin of the penis is to the superficial inguinal and subinguinal lymph nodes. The lymphatics from the glans penis pass to the subinguinal and external iliac nodes. The lymphatics from the proximal urethra drain into the internal iliac (hypogastric) and common iliac lymph nodes (Wood and Angermeier, 2010).

FEMALE URETHRA

Gross Appearance

The adult female urethra is about 4 cm long and 8 mm in diameter. It is slightly curved and lies beneath the pubic symphysis just anterior to the vagina.

Histology

The epithelial lining of the female urethra is squamous in its distal portion and pseudostratified or transitional in the remainder. The submucosa is made up of connective and elastic tissues and spongy venous spaces. Embedded in it are many periurethral glands, which are most numerous distally; the largest of these are the periurethral glands of Skene that open on the floor of the urethra just inside the meatus.

External to the submucosa is a longitudinal layer of smooth muscle continuous with the inner longitudinal layer of the bladder wall. Surrounding this is a heavy layer of circular smooth-muscle fibers extending from the external vesical muscular layer. This constitutes the involuntary internal urethral sphincter. Distal to this is the external striated (voluntary) sphincter surrounding the middle third of the urethra composed of smooth and striated muscles within the midurethra (Ashton-Miller and Delancey, 2009; Morgan et al 2009; Thor and de Groat, 2010).

Blood Supply

The arterial supply to the female urethra is derived from the inferior vesical, vaginal, and internal pudendal arteries. Blood from the urethra drains into the internal pudendal veins.

Lymphatics

Lymphatic drainage from the external portion of the urethra is to the inguinal and subinguinal lymph nodes. Drainage from the deep urethra is into the internal iliac (hypogastric) lymph nodes.

BIBLIOGRAPHY

Adrenals

Avisse C et al: Surgical anatomy and embryology of the adrenal glands. Surg Clin North Am 2000;80:403–415.

O'Donoghue PM et al: Genitourinary imaging: Current and emerging applications. J Postgrad Med 2010;56:131–139.

Kidneys

Budhiraja V et al: Renal artery variations: Embryological basis and surgical correlation. Rom J Morphol Embryol 2010;51:533–536.

Glassberg KI: Normal and abnormal development of the kidney: A clinician's interpretation of current knowledge. J Urol 2002; 167:2339.

Rusinek H et al: Renal magnetic resonance imaging. Curr Opin Nephrol Hypertens 2004;13:667–673.

Calices, Renal Pelvis, and Ureter

Koff SA: Requirements for accurately diagnosing chronic partial upper urinary tract obstruction in children with hydronephrosis. Pediatr Radiol 2008;38(Suppl 1):S41–S48.

Sozen S et al: Significance of lower-pole pelvicaliceal anatomy on stone clearance after shockwave lithotripsy in nonobstructive isolated renal pelvic stones. J Endourol 2008;22(5):877–881.

Bladder

Andersson KE: Detrusor myocyte activity and afferent signaling. Neurourol Urodyn 2010;29(1):97–106.

Berrocal T et al: Anomalies of the distal ureter, bladder, and urethra in children: Embryologic, radiologic, and pathologic features. Radiographics 2002;22:1139.

Birder L et al: Neural control of the lower urinary tract: Peripheral and spinal mechanisms. Neurourol Urodyn 2010;29(1):128–139.

Fry CH, Vahabi B: The role of the mucosa in normal and abnormal bladder function. Basic Clin Pharmacol Toxicol 2016;119(Suppl 3): 57–62.

John H et al: Ultrastructure of the trigone and its functional implications. Urol Int 2001;67(4):264–271.

McCloskey KD: Interstitial cells in the urinary bladder—localization and function. Neurourol Urodyn 2010;29(1):82–87.

Prostate Gland

McNeal JE: The zonal anatomy of the prostate. Prostate 1981;2: 35–49.

Myers RP et al: Making anatomic terminology of the prostate and contiguous structures clinically useful: Historical review and suggestions for revision in the 21st century. Clin Anat 2010;23:18–29.

Raychaudhuri B, Cahill D: Pelvic fasciae in urology. Ann Roy Coll Surg Engl 2008;90:633–637.

Saokar A et al: Detection of lymph nodes in pelvic malignancies with computed tomography and magnetic resonance imaging. Clin Imaging 2010;34:361–366.

Spermatic Cord and Seminal Vesicles

Bhosale PR et al: The inguinal canal: Anatomy and imaging features of common and uncommon masses. Radiographics 2008; 28(3):819–835.

Jen PY et al: Colocalisation of neuropeptides, nitric oxide synthase and immunomarkers for catecholamines in nerve fibres of the adult human vas deferens. J Anat 1999;195(Pt 4):481–489.

Kim B et al: Imaging of the seminal vesicle and vas deferens. Radiographics 2009;29(4):1105–1121.

Testis, Scrotum, and Penis

Bidarkar SS, Hutson JM: Evaluation and management of the abnormal gonad. Semin Pediatr Surg 2005;14:118.

Henry BM et al: Variations in the arterial blood supply to the penis and the accessory pudendal artery: A meta-analysis and review of implications in radical prostatectomy. J Urol 2017;198(2):345–353.

Kim W et al: US MR imaging correlation in pathologic conditions of the scrotum. Radiographics 2007;27(5):1239–1253.

Klonisch T et al: Molecular and genetic regulation of testis descent and external genitalia development. Dev Biol 2004;270:1.

Wood HM, Angermeier KW: Anatomic considerations of the penis, lymphatic drainage, and biopsy of the sentinel node. Urol Clin North Am 2010;37(3):327–334.

Female Urethra

Ashton-Miller JA, Delancey JO: On the biomechanics of vaginal birth and common sequelae. Annu Rev Biomed Eng 2009;11:163–176.

Delancey JO: Why do women have stress urinary incontinence? Neurourol Urodyn 2010;29(Suppl 1):S13–S17.

Morgan et al: Urethral sphincter morphology and function with and without stress incontinence. J Urol 2009;182(1):203–209.

Thor KB, de Groat WC: Neural control of the female urethral and anal rhabdosphincters and pelvic floor muscles. Am J Physiol Regul Integr Compar Physiol 2010;299:R416–R438.

Embryology of the Genitourinary System

2

Emil A. Tanagho, MD; Hiep T. Nguyen, MD;
& Michael DiSandro, MD

At birth, the genital and urinary systems are related only in the sense that they share certain common passages. Embryologically, however, they are intimately related. Because of the complex interrelationships of the embryonic phases of the two systems, they are discussed here as five subdivisions: the nephric system, the vesicourethral unit, the gonads, the genital duct system, and the external genitalia.

NEPHRIC SYSTEM

The nephric system develops progressively as three distinct entities: pronephros, mesonephros, and metanephros.

Pronephros

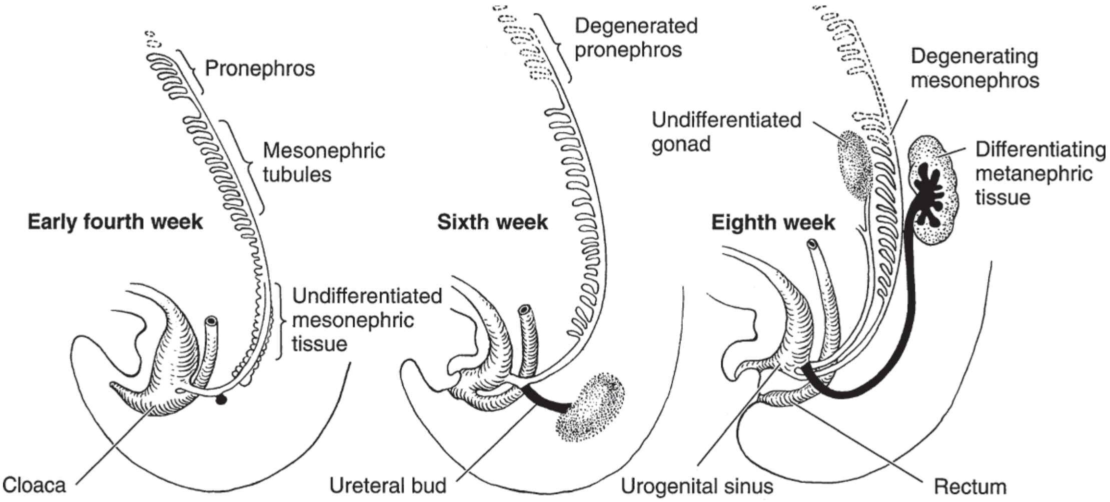
The pronephros is the earliest nephric stage in humans, and it corresponds to the mature structure of the most primitive vertebrate. It extends from the 4th to the 14th somites and consists of 6–10 pairs of tubules. These open into a pair of primary ducts that are formed at the same level, extend caudally, and eventually reach and open into the cloaca. The pronephros is a vestigial structure that disappears completely by the 4th week of embryonic life (Figure 2–1).

Mesonephros

The mature excretory organ of the larger fish and amphibians corresponds to the embryonic mesonephros. It is the principal excretory organ during early embryonic life (4–8 weeks). It, too, gradually degenerates, although parts of its duct system become associated with the male reproductive organs. The mesonephric tubules develop from the intermediate mesoderm caudal to the pronephros shortly before pronephric degeneration. The mesonephric tubules differ from those of the pronephros in that they develop a cuplike outgrowth into which a knot of capillaries is pushed. This is called **Bowman's capsule**, and the tuft of capillaries is called a **glomerulus**. In their growth, the mesonephric tubules extend toward and establish a connection with the nearby primary nephric duct as it grows caudally to join the cloaca (Figure 2–1). This primary nephric duct is now called the **mesonephric duct**. After establishing their connection with the nephric duct, the primordial tubules elongate and become S-shaped. As the tubules elongate, a series of secondary branches increase their surface exposure, thereby enhancing their capacity for interchanging material with the blood in adjacent capillaries. Leaving the glomerulus, the blood is carried by one or more efferent vessels that soon break up into a rich capillary plexus closely related to the mesonephric tubules. The mesonephros, which forms early in the 4th week, reaches its maximum size by the end of the second month.

Metanephros

The metanephros, the final phase of development of the nephric system, originate from both the intermediate mesoderm and the mesonephric duct. Development begins in the 5–6-mm embryo with a budlike outgrowth from the mesonephric duct as it bends to join the cloaca. This ureteral bud grows cephalad and collects mesoderm from the nephrogenic cord of the intermediate mesoderm around its tip. This mesoderm with the metanephric cap moves, with the growing ureteral bud, more and more cephalad from its point of origin. During this cephalic migration, the metanephric cap becomes progressively larger, and rapid internal differentiation takes place. Meanwhile, the cephalic end of the ureteral bud expands within the growing mass of metanephrogenic tissue to form the renal pelvis (Figure 2–1). Numerous outgrowths from the renal pelvic dilatation push radially into this growing mass and form hollow ducts that branch and rebranch as they push toward the periphery. These form the primary collecting ducts of the kidney. Mesodermal cells become arranged in small vesicular masses that lie close to the blind end of the collecting ducts. Each of these vesicular masses will form a uriniferous tubule draining into the duct nearest to its point of origin.



▲ **Figure 2–1.** Schematic representation of the development of the nephric system. Only a few of the tubules of the pronephros are seen early in the 4th week, while the mesonephric tissue differentiates into mesonephric tubules that progressively join the mesonephric duct. During this time, the first sign of the ureteral bud from the mesonephric duct is seen. At 6 weeks, the pronephros has completely degenerated and the mesonephric tubules start to do so. The ureteral bud grows dorsocranially and has met the metanephrogenic cap. At the 8th week, there is cranial migration of the differentiating metanephros. The cranial end of the ureteric bud expands and starts to show multiple successive outgrowths. (Data from several sources.)

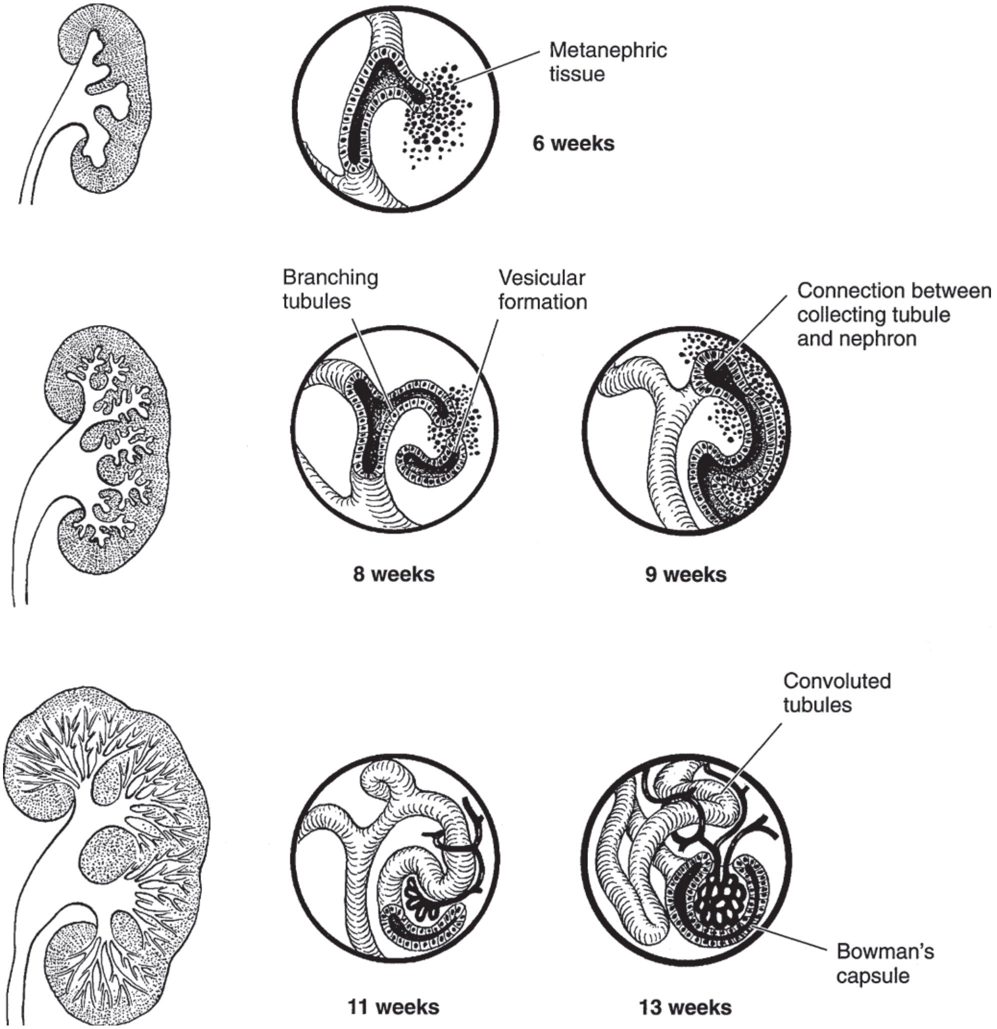
As the kidney grows, increasing numbers of tubules are formed in its peripheral zone. These vesicular masses develop a central cavity and become S-shaped. One end of the S coalesces with the terminal portion of the collecting tubules, resulting in a continuous canal. The proximal portion of the S develops into the distal and proximal convoluted tubules and into Henle's loop; the distal end becomes the glomerulus and Bowman's capsule. At this stage, the undifferentiated mesoderm and the immature glomeruli are readily visible on microscopic examination (Figure 2–2). The glomeruli are fully developed by the 36th week or when the fetus weighs 2500 g (Osathanondh and Potter, 1964a, b). The metanephros arises opposite the 28th somite (fourth lumbar segment). At term, it has ascended to the level of the first lumbar or even the twelfth thoracic vertebra. This ascent of the kidney is due not only to actual cephalic migration but also to differential growth in the caudal part of the body. During the early period of ascent (7th–9th weeks), the kidney slides above the arterial bifurcation and rotates 90°. Its convex border is now directed laterally, not dorsally. Ascent proceeds more slowly until the kidney reaches its final position.

Certain features of these three phases of development must be emphasized: (1) the three successive units of the system develop from the intermediate mesoderm; (2) the tubules at all levels appear as independent primordia and only secondarily unite with the duct system; (3) the nephric duct is laid down as the duct of the pronephros and develops from the union of the ends of the anterior pronephric tubules; (4) this pronephric duct serves subsequently as the mesonephric duct and as such gives rise to the ureter; (5) the nephric duct reaches the cloaca by independent caudal growth; and (6) the embryonic ureter is an outgrowth of the nephric duct, yet the kidney tubules differentiate from adjacent metanephric blastema.

Molecular Mechanisms of Renal and Ureteral Development

The kidney and the collecting system originate from the interaction between the mesonephric duct (Wolffian duct) and the metanephric mesenchyme (MM). The uretic bud (UB) forms as an epithelial outpouching from the mesonephric duct and invades the surrounding MM. Reciprocal induction between the UB and MM results in branching and elongation of the UB from the collecting system and in condensation and epithelial differentiation of MM around the branched tips of the UB. Branching of the UB occurs approximately 15 times during human renal development, generating approximately 300,000 and 1 million nephrons per kidney (Nyengaard and Bendtsen, 1992).

This process of reciprocal induction is dependent on the expression of specific factors. Glial cell-derived neurotrophic factor (GDNF) is the primary inducer of ureteric budding (Costantini and Shakya, 2006). GDNF interacts with several different proteins from the MM (eg, *Wt1, Pax2, Eyal,*



▲ **Figure 2–2.** Progressive stages in the differentiation of the nephrons and their linkage with the branching collecting tubules. A small lump of metanephric tissue is associated with each terminal collecting tubule. These are then arranged in vesicular masses that later differentiate into a uriniferous tubule draining into the duct near which it arises. At one end, Bowman's capsule and the glomerulus differentiate; the other end establishes communication with the nearby collecting tubules.

Six1, Sall1) and from the UB itself (*Pax2, Lim1, Ret*) resulting in outgrowth of the UB (reviewed by Shah et al, 2004). Proper activation of the *Ret*/GDNF signaling pathway in the tip of UB epithelium appears to be essential in the progression of branching morphogenesis (reviewed by Michos, 2009). B-catenin and Gata3 are important regulators of *Ret* expression, and correct activity of *Ret* is regulated by positive (Wnt11 from MM) and negative (Sprouty1 from the UB) feedback signaling. Additional specific factors are required for (1) early branching (eg, *Wnt4 and Wnt11, fgf 7–10*); (2) late branching and maturation (*bmp*2, activin); and (3) branching termination and tubule maintenance (hepatocyte growth factor, transforming growth factor-α, epidermal growth factor receptor) (reviewed by Shah et al, 2004). BMP7, SHH, and Wnt11 produced from the branching ureteric bud induce the MM to differentiate. These factors induce the activation of Pax2, α-8-integrin, and Wnt4 in the renal mesenchymal cells, resulting in condensation of the MM and the formation of pretubular aggregate and primitive renal vesicle (reviewed by Burrow, 2000). With the continued induction from the UB and the autocrine activity of Wnt4, the pretubular aggregates differentiate into comma-shaped bodies. Platelet-derived growth factor α-β and vascular endothelial growth factor expression are required for initiating the migration of endothelial cells into the cleft of the comma-shaped bodies to form rudimentary glomerular capillary tufts (reviewed by Burrow, 2000). Wt1 and *Pod*1 may have important functions in the regulation of gene transcription necessary for the differentiation of podocytes (Ballermann, 2005).

Fibroblast growth factors (FGF) are also important for early metanephric development, especially the receptors Fgfr1 and Fgfr2. A loss of both these receptors leads to kidney agenesis. Other signaling proteins include Six1 and Sall1. Six1 is a homeobox protein essential for early kidney development. Sall1 is a transcription factor that is important for the development of the metanephros. Lack of Sall1 leads to renal agenesis (Krause, 2015).

ANOMALIES OF THE NEPHRIC SYSTEM

Failure of the metanephros to ascend leads to an **ectopic kidney**. An ectopic kidney may be on the proper side but low (simple ectopy) or on the opposite side (crossed ectopy) with or without fusion. Failure to rotate during ascent causes a **malrotated kidney**. Fusion of the paired metanephric masses leads to various anomalies—most commonly a "horseshoe" kidney.

The ureteral bud from the mesonephric duct may bifurcate, causing a **bifid ureter** at various levels depending on the time of the bud's subdivision. An accessory ureteral bud may develop from the mesonephric duct, thereby forming a **duplicated ureter**, usually meeting the same metanephric mass. Rarely, each bud has a separate metanephric mass, resulting in **supernumerary kidneys**.

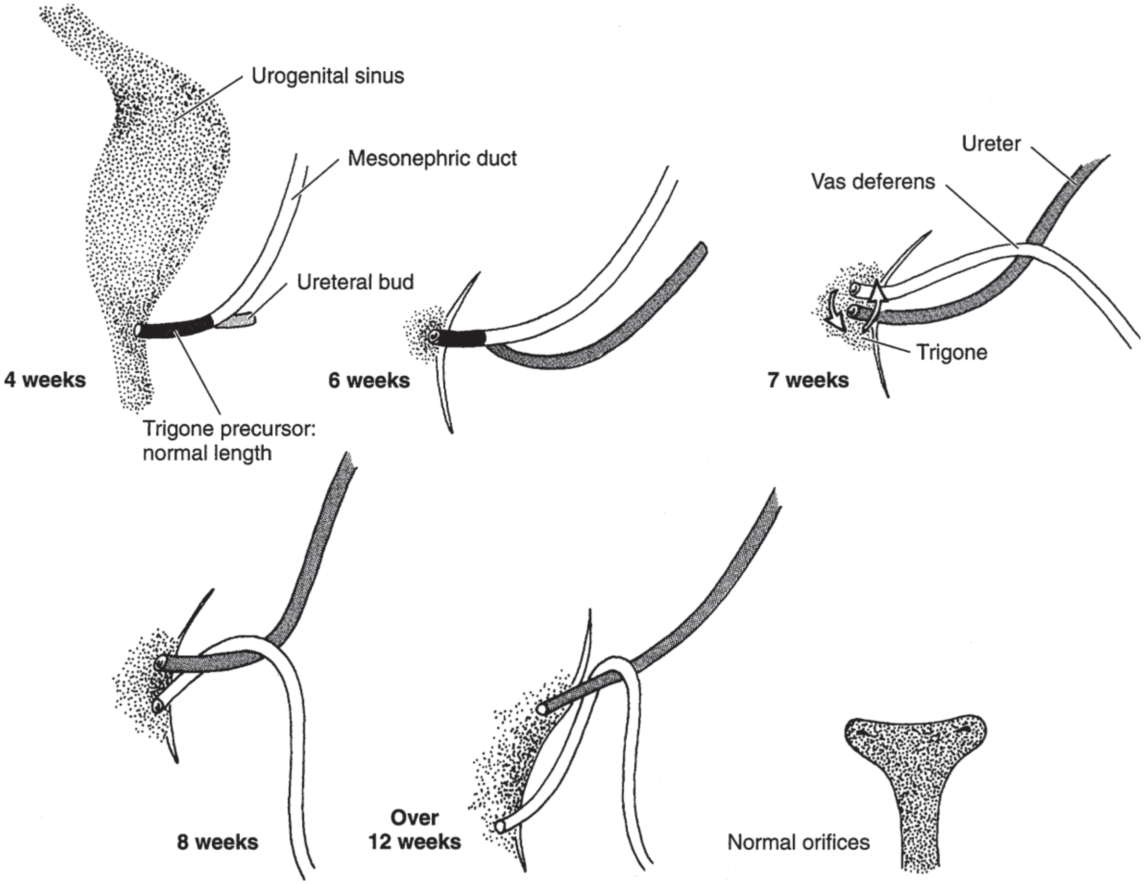
If the double ureteral buds are close together on the mesonephric duct, they open near each other in the bladder. In this case, the main ureteral bud, which is the first to appear and the most caudal on the mesonephric ducts, reaches the bladder first. It then starts to move upward and laterally and is followed later by the second accessory bud as it reaches the urogenital sinus. The main ureteral bud (now more cranial on the urogenital sinus) drains the lower portion of the kidney. The two ureteral buds reverse their relationship as they move from the mesonephric duct to the urogenital sinus. This is why duplicated ureters always cross (Weigert–Meyer law). If the two ureteral buds are widely separated on the mesonephric duct, the accessory bud appears more proximal on the mesonephric duct and therefore ends in the bladder more distal than usual, with an ectopic orifice lower than the normal one. This ectopic orifice could still be in the bladder close to its outlet, in the urethra, or even in the genital duct system (Figure 2–3). A single ureteral bud that arises more proximal than normal on the mesonephric duct can also end in a similar ectopic location, although this is less common.

Lack of development of a ureteral bud results in a **solitary kidney** and a hemitrigone. The ureteral bud may also develop or migrate into the bladder, abnormally leading to a ureterocele. A **ureterocele** is a cystic dilation of the distal intramural ureter and is most commonly associated with an accessory ureteral bud in a duplicated system, but it also can be seen in a single system. The migration and insertion of the ureteric bud into the bladder depend on Ret gene activity and Ret gene expression and is mediated by the action of the retinoic acid and Gata3 gene (Schultza, 2016).

VESICOURETHRAL UNIT

The blind end of the hindgut caudal to the point of origin of the allantois expands to form the cloaca, which is separated from the outside by a thin plate of tissue (the cloacal membrane) lying in an ectodermal depression (the proctodeum) under the root of the tail. At the 4-mm stage, starting at the cephalic portion of the cloaca where the allantois and gut meet, the cloaca progressively divides into two compartments by the caudal growth of a crescentic fold, the urorectal fold. The two limbs of the fold bulge into the lumen of the cloaca from either side, eventually meeting and fusing. The division of the cloaca into a ventral portion (urogenital sinus) and a dorsal portion (rectum) is completed during the 7th week. During the development of the urorectal septum, the cloacal membrane undergoes a reverse rotation, so that the ectodermal surface is no longer directed toward the developing anterior abdominal wall but gradually is turned to face caudally and slightly posteriorly. This change facilitates the subdivision of the cloaca and is brought about mainly by development of the infraumbilical portion of the anterior abdominal wall and regression of the tail. The mesoderm that passes around the cloacal membrane to the caudal attachment of the umbilical cord proliferates and grows, forming a surface elevation, the genital tubercle. Further growth of the infraumbilical part of the abdominal wall progressively separates the umbilical cord from the genital tubercle. The division of the cloaca is completed before the cloacal membrane ruptures, and its two parts therefore have separate openings. The ventral part is the primitive urogenital sinus, which has the shape of an elongated cylinder and is continuous cranially with the allantois; its external opening is the urogenital ostium. The dorsal part is the rectum, and its external opening is the anus.

Traditionally, it is believed that the urogenital sinus receives the mesonephric ducts. The caudal end of the mesonephric duct distal to the ureteral bud (the common excretory duct) is progressively absorbed into the urogenital sinus. By the 7th week, the mesonephric duct and the ureteral bud have independent opening sites. This introduces an island of mesodermal tissue amid the surrounding endoderm of the urogenital sinus. As development progresses, the opening of the mesonephric duct (which will become the ejaculatory duct) migrates downward and medially. The opening of the ureteral bud (which will become the ureteral orifice) migrates upward and laterally. The absorbed mesoderm of the mesonephric duct expands with this migration to occupy the area limited by the final position of these tubes (Figure 2–3). This will later be differentiated as the trigonal structure,



▲ **Figure 2–3.** Development of the ureteral bud from the mesonephric duct and the relationship of both to the urogenital sinus. The ureteral bud appears at the 4th week. The mesonephric duct distal to this ureteral bud is gradually absorbed into the urogenital sinus, resulting in separate endings for the ureter and the mesonephric duct. The mesonephric tissue that is incorporated into the urogenital sinus expands and forms the trigonal tissue.

which is the only mesodermal inclusion in the endodermal vesicourethral unit.

More recent studies suggest an alternative path of development (reviewed by McInnes and Michaud, 2009). The right and left common excretory ducts appear to undergo gradual programmed cell death; the elimination of the common excretory ducts brings the distal ureters into immediate contact with the urogenital sinus epithelium. Concurrently, the ureters undergo a 180° rotation around the axis of the mesonephric duct (also known as the **Wolffian duct**). The distal segment of the ureters then also undergoes apoptosis. As a result, this process generates a new ureteral connection point in the urogenital sinus region that will give rise to the bladder, while the Wolffian duct remains in the region giving rise to the urethra. Further growth of the bladder and urethra moves the ureteral orifices cranially, while those to the Wolffian ducts move caudally. This pattern of development is supported by more recent studies that suggest the trigone is formed mostly from bladder smooth muscle and less so from the ureters. Condensation of myoblasts in the region between the openings of the ureters and Wolffian ducts at 12 weeks of gestation gives rise to the trigone, as a single circular muscular layer and the muscles from the distal ureters cross midline to form the interureteral fold (Oswald et al, 2006).

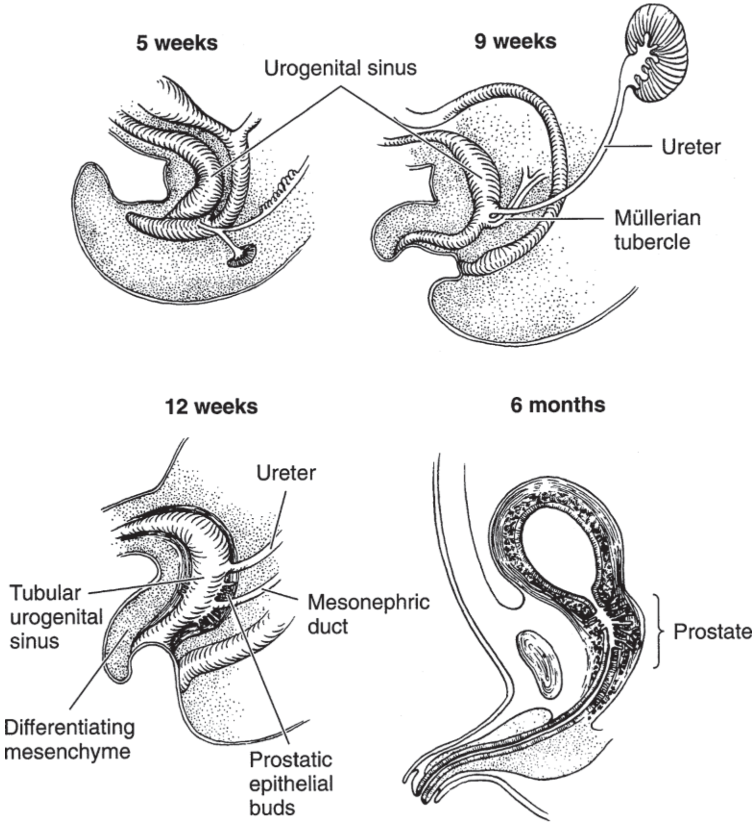
The urogenital sinus can be divided into two main segments. The dividing line, the junction of the combined Müllerian ducts with the dorsal wall of the urogenital sinus, is an elevation called **Müller's tubercle**, which is the most fixed reference point in the whole structure and is discussed in a subsequent section. The segments are as follows:

1. The ventral and pelvic portion forms the bladder, part of the urethra in males, and the whole urethra in females. This portion receives the ureter.

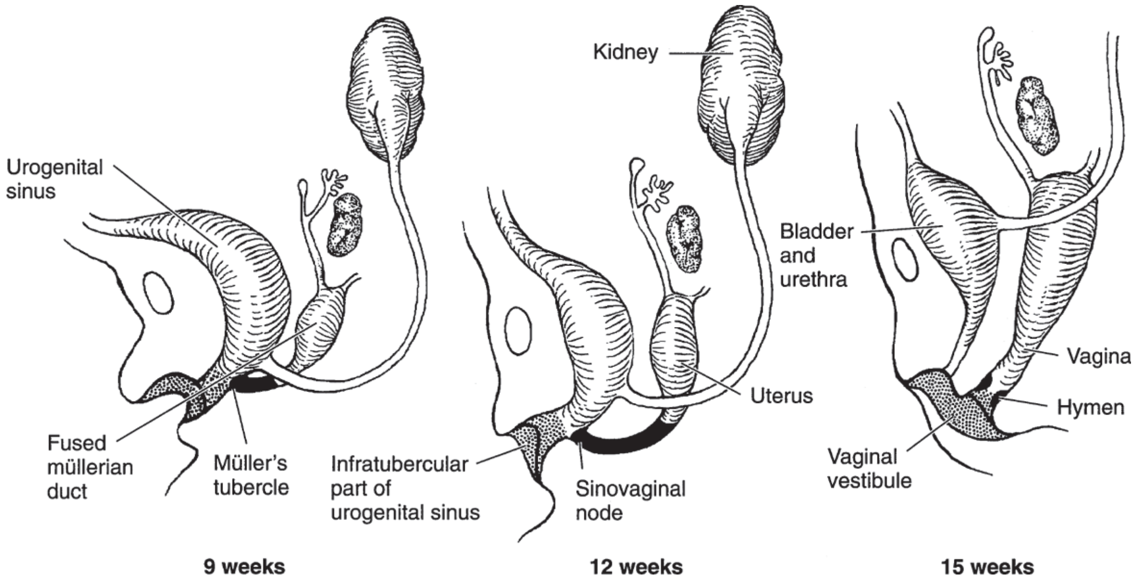
2. The urethral, or phallic, portion receives the mesonephric and the fused Müllerian ducts. This will be part of the urethra in males and forms the lower fifth of the vagina and the vaginal vestibule in females.

During the 3rd month, the ventral part of the urogenital sinus starts to expand and forms an epithelial sac whose apex tapers into an elongated, narrowed urachus. The pelvic portion remains narrow and tubular; it forms the whole urethra in females and the supramontanal portion of the prostatic urethra in males. The splanchnic mesoderm surrounding the ventral and pelvic portion of the urogenital sinus begins to differentiate into interlacing bands of smooth-muscle fibers and an outer fibrous connective tissue coat. By the 12th week, the layers characteristic of the adult urethra and bladder are recognizable (Figure 2–4).

The part of the urogenital sinus caudal to the opening of the Müllerian duct forms the vaginal vestibule and contributes to the lower fifth of the vagina in females (Figure 2–5). In males, it forms the inframontanal part of the prostatic urethra and the membranous urethra. The penile urethra is formed by the fusion of the urethral folds on the ventral surface of the genital tubercle. In females, the urethral folds remain separate and form the labia minora. The glandular urethra in males is formed by canalization of the urethral plate. The bladder originally extends up to the umbilicus, where it is connected to the allantois that extends into the umbilical cord. The allantois usually is obliterated at the level of the umbilicus by the 15th week. The bladder then starts to descend by the 18th week. As it descends, its apex becomes stretched and narrowed, and it pulls on the already obliterated



▲ **Figure 2–4.** Differentiation of the urogenital sinus in males. At the 5th week, the progressively growing urorectal septum separates the urogenital sinus from the rectum. The former receives the mesonephric duct and the ureteral bud. It retains its tubular structure until the 12th week, when the surrounding mesenchyme starts to differentiate into the muscle fibers around the whole structure. The prostate gland develops as multiple epithelial outgrowths just above and below the mesonephric duct. During the 3rd month, the ventral part of the urogenital sinus expands to form the bladder proper; the pelvic part remains narrow and tubular, forming part of the urethra. (Reproduced with permission from Tanagho EA, Smith DR: Mechanism of urinary continence. I. Embryologic, anatomic and pathologic considerations, J Urol. 1968 Nov;100(5):640–646.)



▲ **Figure 2–5.** Differentiation of the urogenital sinus and the Müllerian ducts in the female embryo. At 9 weeks, the urogenital sinus receives the fused Müllerian ducts at Müller's tubercle (sinovaginal node), which is solidly packed with cells. As the urogenital sinus distal to Müller's tubercle becomes wider and shallower (15 weeks), the urethra and fused Müllerian duct will have separate openings. The distal part of the urogenital sinus forms the vaginal vestibule and the lower fifth of the vagina (shaded area), and that part above Müller's tubercle forms the urinary bladder and the entire female urethra. The fused Müllerian ducts form the uterus and the upper four-fifths of the vagina. The hymen is formed at the junction of the sinovaginal node and the urogenital sinus.

allantois, now called the **urachus**. By the 20th week, the bladder is well separated from the umbilicus, and the stretched urachus becomes the middle umbilical ligament.

PROSTATE

The prostate develops as multiple solid outgrowths of the urethral epithelium both above and below the entrance of the mesonephric duct. These simple tubular outgrowths begin to develop in five distinct groups at the end of the 11th week and are complete by the 16th week (112-mm stage). They branch and rebranch, ending in a complex duct system that encounters the differentiating mesenchymal cells around this segment of the urogenital sinus. These mesenchymal cells start to develop around the tubules by the 16th week and become denser at the periphery to form the prostatic capsule. By the 22nd week, the muscular stroma is considerably developed, and it continues to increase progressively until birth.

From the five groups of epithelial buds, five lobes are eventually formed: anterior, posterior, median, and two lateral lobes. Initially, these lobes are widely separated, but later they meet, with no definite septa dividing them. Tubules of each lobe do not intermingle with each other but simply lie side by side.

The anterior lobe tubules begin to develop simultaneously with those of the other lobes. In the early stages, although the anterior lobe tubules are large and show multiple branches, they gradually contract and lose most of the branches. They continue to shrink so that at birth, they show no lumen and appear as small, solid embryonic epithelial outgrowths. In contrast, the tubules of the posterior lobe are fewer in number yet larger, with extensive branching. These tubules, as they grow, extend posterior to the developing median and lateral lobes and form the posterior aspect of the gland, which may be felt rectally.

Prostate development results from complex interaction between urogenital sinus epithelium and mesenchyme in the presence of androgens (reviewed by Cunha et al, 2004, and Thomson, 2008). Early in development, the androgen receptors are solely expressed in the urogenital sinus mesenchyme. Under the influence of androgen, the mesenchyme induces epithelial bud formation, regulates the growth and branching of epithelial bud, promotes differentiation of a secretory epithelium, and specifies differential expression of prostatic secretory proteins. Genome-wide analyses have revealed critical molecular events in prostate development. These include Nkx3.1, Sox, and homeobox genes for ductal morphology development; sonic hedgehog, fibroblast growth factor and the Wnt5a gene for bud development; and bone morphogenic protein and notch genes for branching (Meeks, 2011). Other factors such as activin A serve to inhibit ductal branching in order to maintain tissue homeostasis and regulated growth in the prostate.

ANOMALIES OF THE VESICOURETHRAL UNIT

Failure of the cloaca to subdivide is rare and results in a **persistent cloaca**. Incomplete subdivision is more frequent, ending with **rectovesical**, **rectourethral**, or **rectovestibular fistulas** (usually with **imperforate anus** or **anal atresia**).

Failure of descent or incomplete descent of the bladder leads to a **urinary umbilical fistula** (**urachal fistula**), **urachal cyst**, or **urachal diverticulum** depending on the stage and degree of maldescent.

Development of the genital primordia in an area more caudal than normal can result in formation of the corpora cavernosa just caudal to the urogenital sinus outlet, with the urethral groove on its dorsal surface. This defect results in complete or incomplete **epispadias** depending on its degree. A more extensive defect results in **bladder exstrophy**. Failure of fusion of urethral folds leads to various grades of **hypospadias**. This defect, because of its mechanism, never extends proximal to the bulbous urethra. This is in contrast to epispadias, which usually involves the entire urethra up to the internal meatus.

GONADS

Most of the structures that make up the embryonic genital system have been taken over from other systems, and their readaptation to genital function is a secondary and relatively late phase in their development. The early differentiation of such structures is therefore independent of sexuality. Furthermore, each embryo is at first morphologically bisexual, possessing all the necessary structures for either sex. The development of one set of sex primordia and the gradual involution of the other are determined by the sex of the gonad.

The sexually undifferentiated gonad is a composite structure. Male and female potentials are represented by specific histologic elements (medulla and cortex) that have alternative roles in gonadogenesis. Normal differentiation involves the gradual predominance of one component.

The primitive sex glands appear during the 5th and 6th weeks within a localized region of the thickening known as the urogenital ridge (this contains both the nephric and the genital primordia). At the 6th week, the gonad consists of a superficial germinal epithelium and an internal blastema. The blastemal mass is derived mainly from proliferative ingrowth from the superficial epithelium, which comes loose from its basement membrane.

During the 7th week, the gonad begins to assume the characteristics of a testis or ovary. Differentiation of the ovary usually occurs somewhat later than differentiation of the testis.

If the gonad develops into a testis, the gland increases in size and shortens into a more compact organ while achieving a more caudal location. Its broad attachment to the mesonephros is converted into a gonadal mesentery known as the **mesorchium**. The cells of the germinal epithelium grow into the underlying mesenchyme and form cordlike masses. These are radially arranged and converge toward the mesorchium, where a dense portion of the blastemal mass is also emerging as the primordium of the rete testis. A network of strands soon forms that is continuous with the testis cords. The latter also split into three to four daughter cords. These eventually become differentiated into the seminiferous tubules by which the spermatozoa are produced. The rete testis unites with the mesonephric components that will form the male genital ducts, as discussed in a subsequent section (Figure 2–6).

If the gonad develops into an ovary, it (like the testis) gains a mesentery (mesovarium) and settles in a more caudal position. During the 9th week the internal blastema differentiates in the into a primary cortex beneath the germinal epithelium and a loose primary medulla. A compact cellular mass bulges from the medulla into the mesovarium and establishes the primitive rete ovarii. At 3–4 months of age, the internal cell mass becomes young ova. A new definitive cortex is formed from the germinal epithelium as well as from the blastema in the form of distinct cellular cords (Pflüger's tubes), and a permanent medulla is formed. The cortex differentiates into ovarian follicles containing ova.

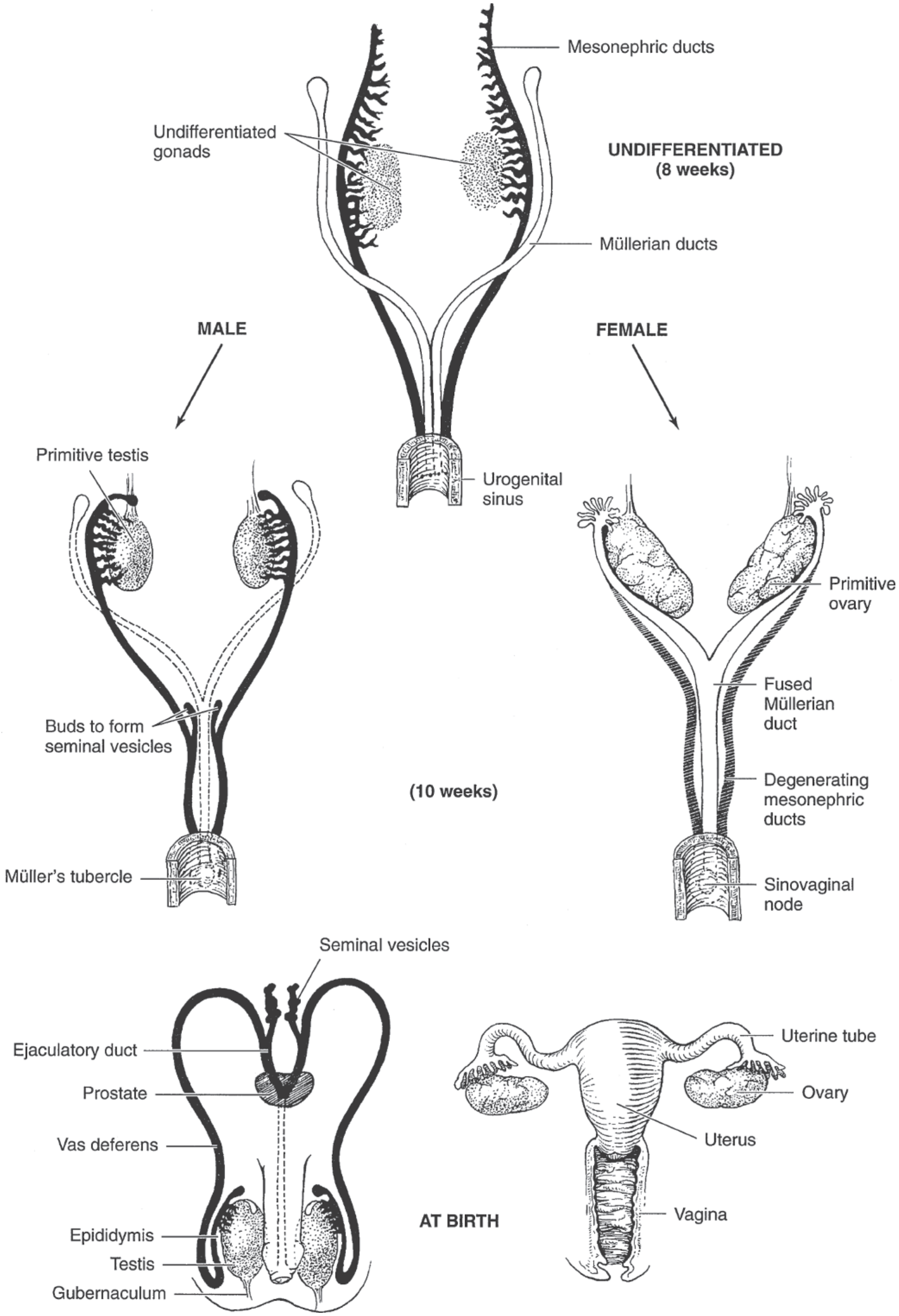
Genetically, in the presence of a Y chromosome, SRY (as known as testis determining factor [TDF]) induces the upregulation of *Sox*9 in the undifferentiated gonad (reviewed by Sekido, 2010). This in turn upregulates the expression of FGF9 and increases PGD2 synthesis, both helping to maintain *Sox*9 expression. *Sox*9 directs the differentiation of cells into Sertoli cell by activating several downstream genes such as *Amh*, *Cbln*4, FGF9, and *Ptgds*. In the absence of a Y chromosome and SRY, *Rspo*1 is upregulated in the undifferentiated gonads (reviewed by Nef and Vassalli, 2009). *Rspo*1 is required for Wnt4 expression, and together they activate β-catenin, which, in turn, suppresses the formation of the testis cords by inhibiting *Sox*9 and FGF9. A second pathway involving the upregulation of *Foxl*2 also serves to inhibit *Sox* 9 and FGF9 activity, contributing to the development of the ovary.

New genetic data on human sex determination from modern gene sequencing will create opportunities for the development of mechanistic models and should lead to better understanding of this complex process (reviewed by Bashamboo, 2017).

Descent of the Gonads

A. Testis

In addition to its early caudal migration, the testis later leaves the abdominal cavity and descends into the scrotum. By the 3rd month of fetal life, the testis is located retroperitoneally in the false pelvis. A fibromuscular band (the gubernaculum) extends from the lower pole of the testis through the developing muscular layers of the anterior abdominal wall



▲ **Figure 2–6.** Transformation of the undifferentiated genital system into the definitive male and female systems.

to terminate in the subcutaneous tissue of the scrotal swelling. The gubernaculum also has several other subsidiary strands that extend to adjacent regions. Just below the lower pole of the testis, the peritoneum herniates as a diverticulum along the anterior aspect of the gubernaculum, eventually reaching the scrotal sac through the anterior abdominal muscles (the processus vaginalis). The testis remains at the abdominal end of the inguinal canal until the 7th month. It then passes through the inguinal canal behind (but invaginating) the processus vaginalis. Normally, it reaches the scrotal sac by the end of the 8th month.

B. Ovary

In addition to undergoing an early internal descent, the ovary becomes attached through the gubernaculum to the tissues of the genital fold and then attaches itself to the developing uterovaginal canal at its junction with the uterine (fallopian) tubes. This part of the gubernaculum between the ovary and uterus becomes the ovarian ligament; the part between the uterus and the labia majora becomes the round ligament of the uterus. These ligaments prevent extra-abdominal descent, and the ovary enters the true pelvis. It eventually lies posterior to the uterine tubes on the superior surface of the urogenital mesentery, which has descended with the ovary and now forms the broad ligament. A small processus vaginalis forms and passes toward the labial swelling, but it is usually obliterated at full term.

GONADAL ANOMALIES

The gonad may either (1) not develop (agenesis), (2) develop incompletely (hypogenesis), (3) develop incorrectly (dysgenesis), or (4) develop correctly, but then suffer an embryologic injury (eg, intrauterine torsion). **Supernumerary gonads** are rare. The commonest anomaly involves descent of the gonads, especially the testis. Retention of the testis in the abdomen or arrest of its descent at any point along its natural pathway is called **cryptorchidism**, which may be either unilateral or bilateral. If the testis does not follow the main gubernacular structure but follows one of its subsidiary strands, it will end in an abnormal position, resulting in an **ectopic testis**.

Failure of union between the rete testis and mesonephros results in a testis separate from the male genital ducts (the epididymis) and azoospermia.

GENITAL DUCT SYSTEM

Alongside the indifferent gonads, there are, early in embryonic life, two different yet closely related ducts. One is primarily a nephric duct (Wolffian duct), yet it also serves as a genital duct if the embryo develops into a male. The other (Müllerian duct) is primarily a genital structure from the start.

Both ducts grow caudally to join the primitive urogenital sinus. The Wolffian duct (known as the **pronephric duct** at the 4-mm stage) joins the ventral part of the cloaca, which will be the urogenital sinus. This duct gives rise to the ureteral bud close to its caudal end. The ureteral bud grows cranially and meets metanephrogenic tissue. The part of each mesonephric duct caudal to the origin of the ureteric bud becomes absorbed into the wall of the primitive urogenital sinus so that the mesonephric duct and ureter open independently. This is achieved at the 15-mm stage (7th week). During this period, starting at the 10-mm stage, the Müllerian ducts start to develop. They reach the urogenital sinus relatively late—at the 30-mm stage (9th week); their partially fused blind ends producing the elevation called **Müller's tubercle**. Müller's tubercle is the most constant and reliable point of reference in the whole system.

If the gonad starts to develop into a testis (17-mm stage, 7th week), the Wolffian duct will start to differentiate into the male duct system, forming the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts, when the Müllerian duct proceeds toward its junction with the urogenital sinus and immediately starts to degenerate. Only its upper and lower ends persist, the former as the appendix testis and the latter as part of the prostatic utricle.

If the gonad starts to differentiate into an ovary (22-mm stage, 8th week), the Müllerian duct system forms the uterine (fallopian) tubes, uterus, and most of the vagina. The Wolffian ducts, aside from their contribution to the urogenital sinus, remain rudimentary.

MALE DUCT SYSTEM

▶ Epididymis

Because of the proximity of the differentiating gonads and the nephric duct, some of the mesonephric tubules are retained as the efferent ductules, and their lumens become continuous with those of the rete testis. These tubules, together with the part of the mesonephric duct into which they empty, will form the epididymis. Each coiled ductule makes a conical mass known as the **lobule of the epididymis**. The cranial end of the mesonephric duct becomes highly convoluted, completing the formation of the epididymis. This is an example of direct inclusion of a nephric structure into the genital system. Additional mesonephric tubules, both cephalad and caudal to those that were included in the formation of the epididymis, remain as rudimentary structures, that is, the appendix of the epididymis and the paradidymis.

▶ Vas Deferens, Seminal Vesicles, and Ejaculatory Ducts

The mesonephric duct caudal to the portion forming the epididymis forms the vas deferens. Shortly before this duct joins the urethra (urogenital sinus), a localized dilatation (ampulla) develops, and the saccular convoluted structure that will form the seminal vesicle is evaginated from its wall. The mesonephric duct between the origin of the seminal vesicle and the urethra forms the ejaculatory duct. The whole mesonephric duct now achieves its characteristic thick investment of smooth muscle, with a narrow lumen along most of its length.

Both above and below the point of entrance of the mesonephric duct into the urethra, multiple outgrowths of urethral epithelium mark the beginning of the development of the prostate. As these epithelial buds grow, they meet the developing muscular fibers around the urogenital sinus, and some of these fibers become entangled in the branching tubules of the growing prostate and become incorporated into it, forming its muscular stroma (Figure 2–4).

FEMALE DUCT SYSTEM

The Müllerian ducts, which are a paired system, are seen alongside the mesonephric duct. It is not known whether they arise directly from the mesonephric ducts or separately as an invagination of the celomic epithelium into the parenchyma lateral to the cranial extremity of the mesonephric duct, but the latter theory is favored. The Müllerian duct develops and runs lateral to the mesonephric duct. Its opening into the celomic cavity persists as the peritoneal ostium of the uterine tube (later it develops fimbriae). The other end grows caudally as a solid tip and then crosses in front of the mesonephric duct at the caudal extremity of the mesonephros. It continues its growth in a caudomedial direction until it meets and fuses with the Müllerian duct of the opposite side. The fusion is partial at first, so there is a temporary septum between the two lumens. This later disappears, leaving one cavity that will form the uterovaginal canal. The potential lumen of the vaginal canal is completely packed with cells. The solid tip of this cord pushes the epithelium of the urogenital sinus outward, where it becomes Müller's tubercle (33-mm stage, 9th week). The Müllerian ducts fuse at the 63-mm stage (13th week), forming the sinovaginal node, which receives a limited contribution from the urogenital sinus (this contribution forms the lower fifth of the vagina).

The urogenital sinus distal to Müller's tubercle, originally narrow and deep, shortens, widens, and opens to form the floor of the pudendal or vulval cleft. This results in separate openings for the vagina and urethra and brings the vaginal orifice to its final position nearer the surface. At the same time, the vaginal segment increases appreciably in length. The vaginal vestibule is derived from the infratubercular segment of the urogenital sinus (in males, the same segment will form the inframontanal part of the prostatic urethra and the membranous urethra). The labia minora are formed from the urethral folds (in males they form the pendulous urethra). The hymen is the remnant of the Müllerian tubercle. The lower fifth of the vagina is derived from the portion of the urogenital sinus that combines with the sinovaginal node. The remainder of the vagina and the uterus are formed from the lower (fused) third of the Müllerian ducts. The uterine tubes (fallopian tubes, oviducts) are the cephalic two-thirds of the Müllerian ducts (Figure 2–6).

ANOMALIES OF THE GONADAL DUCT SYSTEM

Nonunion of the rete testis and the efferent ductules can occur and, if bilateral, causes **azoospermia** and **sterility**. Failure of the Müllerian ducts to approximate or to fuse completely can lead to various degrees of **duplication** in the genital ducts. **Congenital absence** of one or both uterine tubes or of the uterus or vagina occurs rarely.

Arrested development of the infratubercular segment of the urogenital sinus leads to its persistence, with the urethra and vagina having a common duct to the outside (**urogenital sinus**).

EXTERNAL GENITALIA

During the 8th week, external sexual differentiation begins to occur. Not until 3 months, however, do the progressively developing external genitalia attain characteristics that can be recognized as distinctively male or female. During the indifferent stage of sexual development, three small protuberances appear on the external aspect of the cloacal membrane. In front is the genital tubercle, and on either side of the membrane are the genital swellings.

With the breakdown of the urogenital membrane (17-mm stage, 7th week), the primitive urogenital sinus achieves a separate opening on the undersurface of the genital tubercle.

MALE EXTERNAL GENITALIA

The urogenital sinus opening extends on the ventral aspect of the genital tubercle as the urethral groove. The primitive urogenital orifice and the urethral groove are bound on either side by the urethral folds. The genital tubercle becomes elongated to form the phallus. The corpora cavernosa is indicated in the 7th week as paired mesenchymal columns within the shaft of the penis. By the 10th week, the urethral folds start to fuse from the urogenital sinus orifice toward the tip of the phallus. At the 14th week, the fusion is complete and results in the formation of the penile urethra. The corpus spongiosum results from the differentiation of the mesenchymal masses around the formed penile urethra.

The glans penis becomes defined by the development of a circular coronary sulcus around the distal part of the phallus. The urethral groove and the fusing folds do not extend beyond the coronary sulcus. The glandular urethra develops as a result of canalization of an ectodermal epithelial cord that has grown through the glans. This canalization reaches and communicates with the distal end of the previously formed penile urethra. During the 3rd month, a fold of skin at the base of the glans begins growing distally and, 2 months later, surrounds the glans. This forms the prepuce. Meanwhile, the genital swellings shift caudally and are recognizable as scrotal swellings. They meet and fuse, resulting in the formation of the scrotum, with two compartments partially separated by a median septum and a median raphe, indicating their line of fusion.

FEMALE EXTERNAL GENITALIA

Until the 8th week, the appearance of the female external genitalia closely resembles that of the male genitalia except that the urethral groove is shorter. The genital tubercle, which becomes bent caudally and lags in development, becomes the clitoris. As in males (albeit on a minor scale), mesenchymal columns differentiate into corpora cavernosa, and a coronary sulcus identifies the glans clitoridis. The most caudal part of the urogenital sinus shortens and widens, forming the vaginal vestibule. The urethral folds do not fuse but remain separate as the labia minora. The genital swellings meet in front of the anus, forming the posterior commissure, while the swellings enlarge and remain separated on either side of the vestibule and form the labia majora.

ANOMALIES OF THE EXTERNAL GENITALIA

Absence or duplication of the penis or clitoris is very rare. More commonly, the penis remains rudimentary or the clitoris shows hypertrophy. These anomalies may be seen alone or, more frequently, in association with differences of sex development (DSD). Concealed penis and transposition of penis and scrotum are relatively rare anomalies.

Failure or incomplete fusion of the urethral folds results in **hypospadias** (see preceding discussion). Penile development is also anomalous in cases of **epispadias** and **exstrophy** (see preceding discussion).

BIBLIOGRAPHY

General

Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology. 7th ed. Saunders, Philadelphia, 1974.

Ballermann BJ: Glomerular endothelial cell differentiation. Kidney Int 2005;67(5):1668–1671.

Burrow CR: Regulatory molecules in kidney development. Pediatr Nephrol 2000;131(7):240–253.

Carlson BM: Patten's Foundations of Embryology. 6th ed. McGraw-Hill, New York, 1996.

Costantini F, Shakya R: GDNF/Ret signaling and the development of the kidney. Bioessays 2006;28(2):117–127.

Cunha GR et al: Hormonal, cellular, and molecular regulation of normal and neoplastic prostatic development. J Steroid Biochem Mol Biol 2004;92(4):221–236.

Fine RN: Diagnosis and treatment of fetal urinary tract abnormalities. J Pediatr 1992;121:333.

FitzGerald MJT: Human Embryology: A Regional Approach. Harper & Row, London, 1978.

Gilbert SG: Pictorial Human Embryology. University of Washington Press, Seattle, 1989.

Marshall FF: Embryology of the lower genitourinary tract. Urol Clin North Am 1978;5:3.

Michos O: Kidney development: From ureteric bud formation to branching morphogenesis. Curr Opin Genet Dev 2009;19:484–490.

Mcinnes RR, Michaud JL: Plumbing in the embryo: Development defects of the urinary tracts. Clin Genet 2009;75:307–317.

Nef S, Vassalli JD: Complementary pathways in mammalian female sex determination. J Biol 2009;8:74.

Nyengaard JR, Bendtsen TF: Glomerular number and size in relation to age, kidney weight, and body surface in normal man. Anat Rec 1992;232(2):194–201.

Oswald J et al: Reevaluation of the fetal muscle development of the vesical trigone. J Urol 2006;176(3):1166–1170.

Reddy PP, Mandell J: Prenatal diagnosis: Therapeutic implications. Urol Clin North Am 1998;25:171.

Sekido R: SRY: A transcriptional activator of mammalian testis determination. Int J Biochem Cell Biol 2010;42(3):417–420.

Shah MM et al: Branching morphogenesis and kidney disease. Development 2004;131(7):1449–1462.

Stephens FD: Embryopathy of malformations. J Urol 1982;127:13.

Stephens FD: Congenital Malformations of the Urinary Tract. Praeger, New York, 1983.

Tanagho EA: Embryologic development of the urinary tract. In: Ball TP (ed): AUA Update Series. American Urological Association, Philadelphia, 1982.

Tanagho EA: Developmental anatomy and urogenital abnormalities. In: Raz S (ed): Female Urology. 2nd ed. Saunders, Philadelphia, 1986.

Thomson AA: Mesenchymal mechanisms in prostate organogenesis. Differentiation 2008;76(6):587–598.

Vaughan ED Jr, Middleton GW: Pertinent genitourinary embryology: Review for practicing urologist. Urology 1975;6:139.

Anomalies of the Nephric System

Avni EF et al: Multicystic dysplastic kidney: Natural history from in utero diagnosis and postnatal followup. J Urol 1987;138:1420.

Bomalaski MD et al: Vesicoureteral reflux and ureteropelvic junction obstruction: Association, treatment options and outcome. J Urol 1997;157:969.

Chevalier RL: Effects of ureteral obstruction on renal growth. Pediatr Nephrol 1995;9:594.

Churchill BM et al: Ureteral duplication, ectopy and ureteroceles. Pediatr Clin North Am 1987;34:1273.

Corrales JG, Elder JS: Segmental multicystic kidney and ipsilateral duplication anomalies. J Urol 1996;155:1398.

Cox R et al: Twenty-year follow-up of primary megaureter. Eur Urol 1990;17:43.

Decter RM: Renal duplication and fusion anomalies. Pediatr Clin North Am 1997;44:1323.

El-Galley RE, Keane TE: Embryology, anatomy, and surgical applications of the kidney and ureter. Surg Clin North Am 2000;80:381.

Glassberg KI: Normal and abnormal development of the kidney: A clinician's interpretation of current knowledge. J Urol 2002;167:2339.

Keating MA et al: Changing concepts in management of primary obstructive megaureter. J Urol 1989;142:636.

Krause M et al: Signaling during kidney development. Cells 2015;4(2):112.

MacDermot KD et al: Prenatal diagnosis of autosomal dominant polycystic kidney disease (PKD1) presenting in utero and prognosis for very early onset disease. J Med Genet 1998;35:13.

Magee MC: Ureteroceles and duplicated systems: Embryologic hypothesis. J Urol 1980;123:605.

Maher ER, Kaelin WG Jr: Von Hippel-Lindau disease. Medicine (Baltimore) 1997;76:381.

Mesrobian HG et al: Unilateral renal agenesis may result from in utero regression of multicystic renal dysplasia. J Urol 1993; 150:793.

Murcia NS et al: New insights into the molecular pathophysiology of polycystic kidney disease. Kidney Int 1999;55:1187.

Nguyen HT, Kogan BA: Upper urinary tract obstruction: Experimental and clinical aspects. Br J Urol 1998;81(Suppl 2):13.

Osathanondh V, Potter EL: Pathogenesis of polycystic kidneys: Survey of results of microdissection. Arch Pathol 1964a;77:510.

Osathanondh V, Potter EL: Pathogenesis of polycystic kidneys: Type 4 due to urethral obstruction. Arch Pathol 1964b;77:502.

Pope JC IV et al: How they begin and how they end: Classic and new theories for the development and deterioration of congenital anomalies of the kidney and urinary tract, CAKUT. J Am Soc Nephrol 1999;10:2018.

Prasad PV, Priatna A: Functional imaging of the kidneys with fast MRI techniques. Eur J Radiol 1999;29:133.

Robson WL et al: Unilateral renal agenesis. Adv Pediatr 1995;42:575.

Ross JH, Kay R: Ureteropelvic junction obstruction in anomalous kidneys. Urol Clin North Am 1998;25:219.

Scherz HC et al: Ectopic ureteroceles: Surgical management with preservation of continence. Review of 60 cases. J Urol 1989;142:538.

Soderdahl DW et al: Bilateral ureteral quadruplication. J Urol 1976; 116:255.

Somlo S, Markowitz GS: The pathogenesis of autosomal dominant polycystic kidney disease: An update. Curr Opin Nephrol Hypertens 2000;9:385.

Tanagho EA: Ureteroceles: Embryogenesis, pathogenesis and management. J Cont Educ Urol 1979;18:13.

Tanagho EA: Development of the ureter. In: Bergman H (ed): The Ureter. 2nd ed. Springer-Verlag, New York, 1981.

Thomsen HS et al: Renal cystic diseases. Eur Radiol 1997;7:1267.

Tokunaka S et al: Morphological study of ureterocele: Possible clue to its embryogenesis as evidenced by locally arrested myogenesis. J Urol 1981;126:726.

Zerres K et al: Autosomal recessive polycystic kidney disease. Contrib Nephrol 1997;122:10.

Anomalies of the Vesicourethral Unit

Asopa HS: Newer concepts in the management of hypospadias and its complications. Ann Roy Coll Surg Engl 1998;80:161.

Austin PF et al: The prenatal diagnosis of cloacal exstrophy. J Urol 1998;160(3, Pt 2):1179.

Baskin LS: Hypospadias and urethral development. J Urol 2000; 163:951.

Begg RC: The urachus, its anatomy, histology and development. J Anat 1930;64:170.

Belman AB: Hypospadias update. Urology 1997;49:166.

Burbige KA et al: Prune belly syndrome: 35 years of experience. J Urol 1987;137:86.

Churchill BM et al: Emergency treatment and long-term follow-up of posterior urethral valves. Urol Clin North Am 1990;17:343.

Chwalle R: The process of formation of cystic dilatations of the vesicle end of the ureter and of diverticula at the ureteral ostium. Urol Cutan Rev 1927;31:499.

Connor JP et al: Long-term follow-up of 207 patients with bladder exstrophy: An evolution in treatment. J Urol 1989;142:793.

Dinneen MD, Duffy PG: Posterior urethral valves. Br J Urol 1996; 78:275.

Duckett JW: The current hype in hypospadiology. Br J Urol 1995; 76(Suppl 3):1.

Eagle JR Jr, Barrett GS: Congenital deficiency of abdominal musculature with associated genitourinary abnormalities: A syndrome. Report of nine cases. Pediatrics 1950;6:721.

Elmassalme FN et al: Duplication of urethra—case report and review of literature. Eur J Pediatr Surg 1997;7:313.

Escham W, Holt HA: Complete duplication of bladder and urethra. J Urol 1980;123:773.

Goh DW et al: Bladder, urethral, and vaginal duplication. J Pediatr Surg 1995;30:125.

Greskovich FJ III, Nyberg LM Jr: The prune belly syndrome: A review of its etiology, defects, treatment and prognosis. J Urol 1988;140:707.

Hinman F Jr: Surgical disorders of the bladder and umbilicus of urachal origin. Surg Gynecol Obstet 1961;113:605.

Jaramillo D et al: The cloacal malformation: Radiologic findings and imaging recommendations. Radiology 1990;177:441.

Jeffs RD: Exstrophy, epispadias, and cloacal and urogenital sinus abnormalities. Pediatr Clin North Am 1987;34:1233.

Landes RR et al: Vesical exstrophy with epispadias: Twenty-year follow-up. Urology 1977;9:53.

Mackie GG: Abnormalities of the ureteral bud. Urol Clin North Am 1978;5:161.

Manzoni GA et al: Cloacal exstrophy and cloacal exstrophy variants: A proposed system of classification. J Urol 1987;138:1065.

Massad CA et al: Morphology and histochemistry of infant testes in the prune belly syndrome. J Urol 1991;146:1598.

Meeks J et al: Genetic regulation of prostate development. J Andrology 2011;32(3):210.

Mesrobian HG et al: Long-term followup of 103 patients with bladder exstrophy. J Urol 1988;139:719.

Mouriquand PD et al: Hypospadias repair: Current principles and procedures. Br J Urol 1995;76(Suppl 3):9.

Nguyen HT, Kogan BA: Fetal bladder physiology. Adv Exp Med Biol 1999;462:121.

Orvis BR et al: Testicular histology in fetuses with the prune belly syndrome and posterior urethral valves. J Urol 1988;139:335.

Randall A, Campbell EW: Anomalous relationship of the right ureter to the vena cava. J Urol 1935;34:565.

Rosenfeld B et al: Type III posterior urethral valves: Presentation and management. J Pediatr Surg 1994;29:81.

Schultza K et al: Genetic basis of ureterocele. Curr Genom 2016; 17(1):62.

Shapiro E: Embryologic development of the prostate: Insights into the etiology and treatment of benign prostatic hyperplasia. Urol Clin North Am 1990;17:487.

Silver RI: What is the etiology of hypospadias? A review of recent research. Delaware Med J 2000;72:343.

Stein R, Thuroff JW: Hypospadias and bladder exstrophy. Curr Opin Urol 2002;12:195.

Stephens FD: The female anus, perineum and vestibule: Embryogenesis and deformities. J Obstet Gynaecol Br Commonw 1968; 8:55.

Tanagho EA: Embryologic basis for lower ureteral anomalies: A hypothesis. Urology 1976;7:451.

Uehling DT: Posterior urethral valves: Functional classification. Urology 1980;15:27.

Van Savage JG et al: An algorithm for the management of anterior urethral valves. J Urol 1997;158(3, Pt 2):1030.

Wakhlu AK et al: Congenital megalourethra. J Pediatr Surg 1996; 31:441.

Workman SJ, Kogan BA: Fetal bladder histology in posterior urethral valves and the prune belly syndrome. J Urol 1990;144:337.

Gonadal Anomalies

Barteczko KJ, Jacob MI: The testicular descent in humans: Origin, development and fate of the gubernaculum Hunteri, processus vaginalis peritonei, and gonadal ligaments. Adv Anat Embryol Cell Biol 2000;156: III–X, 1.

Bashamboo A et al: Anomalies in human sex determination provide unique insights into the complex genetic interactions of early gonad development. Clin Genet 2017;91(2):143.

Belville C et al: Persistence of Müllerian derivatives in males. Am J Med Genet 1999;89:218?

Ben-Chaim J, Gearhart JP: Current management of bladder exstrophy. Scand J Urol Nephrol 1997;31:103.

Borzi PA, Thomas DF: Cantwell-Ransley epispadias repair in male epispadias and bladder exstrophy. J Urol 1994;151:457.

Crankson SJ, Ahmed S: Female bladder exstrophy. Int Urogynecol J Pelvic Floor Dysfunct 1997;8:98.

de Palma L et al: Epididymal and vas deferens immaturity in cryptorchidism. J Urol 1988;140:1166.

Diez Garcia R et al: Peno-scrotal transposition. Eur J Pediatr Surg 1995;5:222.

Elder JS et al: Androgenic sensitivity of gubernaculum testis: Evidence for hormonal/mechanical interactions in testicular descent. J Urol 1982;127:170.

Gad YZ et al: 5 alpha-reductase deficiency in patients with micropenis. J Inherit Metab Dis 1997;20:95.

Hadziselimovic F et al: The significance of postnatal gonadotropin surge for testicular development in normal and cryptorchid testes. J Urol 1986;136:274.

Honoré LH: Unilateral anorchism: Report of 11 cases with discussion of etiology and pathogenesis. Urology 1978;11:251.

Johnson P et al: Inferior vesical fissure. J Urol 1995;154:1478.

Mollard P et al: Female epispadias. J Urol 1997;158:1543.

Nef S, Parada LF: Hormones in male sexual development. Genes Dev 2000;14:3075.

Newman K et al: The surgical management of infants and children with ambiguous genitalia: Lessons learned from 25 years. Ann Surg 1992;215:644.

Pagon RA: Diagnostic approach to the newborn with ambiguous genitalia. Pediatr Clin North Am 1987;34:1019.

Parker KL et al: Gene interactions in gonadal development. Annu Rev Physiol 1999;61:417.

Rajfer J, Walsh PC: Testicular descent: Normal and abnormal. Urol Clin North Am 1978;5:223.

Toppari J, Kaleva M: Maldescendus testis. Horm Res 1999;51:261.

Zaontz MR, Packer MG: Abnormalities of the external genitalia. Pediatr Clin North Am 1997;44:1267.

Symptoms of Disorders of the Genitourinary Tract

3

Benjamin N. Breyer, MD, MAS, FACS

In the workup of any patient, the history is of paramount importance; this is particularly true in urology. It is necessary to discuss here only those urologic symptoms that are apt to be brought to the physician's attention by the patient. It is important to know not only whether the disease is acute or chronic but also whether it is recurrent, since recurring symptoms may represent acute exacerbations of chronic disease.

Obtaining the history is an art that depends on the skill and methods used to elicit information. The history is only as accurate as the patient's ability to describe the symptoms. This subjective information is important in establishing an accurate diagnosis.

SYSTEMIC MANIFESTATIONS

Symptoms of fever and weight loss should be sought. The presence of fever associated with other symptoms of urinary tract infection may be helpful in evaluating the site of the infection. Simple acute cystitis is essentially an afebrile disease. Acute pyelonephritis or prostatitis is apt to cause high temperatures (≤40°C [104°F]), often accompanied by violent chills. Infants and children who have acute pyelonephritis may have high temperatures without other localizing symptoms or signs. Such a clinical picture, therefore, *invariably* requires bacteriologic study of the urine.

A history of unexplained attacks of fever occurring even years before may otherwise represent asymptomatic pyelonephritis. Renal carcinoma sometimes causes fever that may reach 39°C (102.2°F) or more. The absence of fever does not by any means rule out renal infection, for it is the rule that chronic pyelonephritis does not cause fever.

Weight loss is to be expected in the advanced stages of cancer, but it may also be noticed when renal insufficiency due to obstruction or infection supervenes. In children who have "failure to thrive" (low weight and less than average height for their age), chronic obstruction, urinary tract infection, or both should be suspected.

General malaise may be noted with tumors, chronic pyelonephritis, or renal failure. The presence of many of these symptoms may be compatible with human immunodeficiency virus (HIV; see Chapter 17).

LOCAL AND REFERRED PAIN

Two types of pain have their origins in the genitourinary organs: local and referred. The latter is especially common.

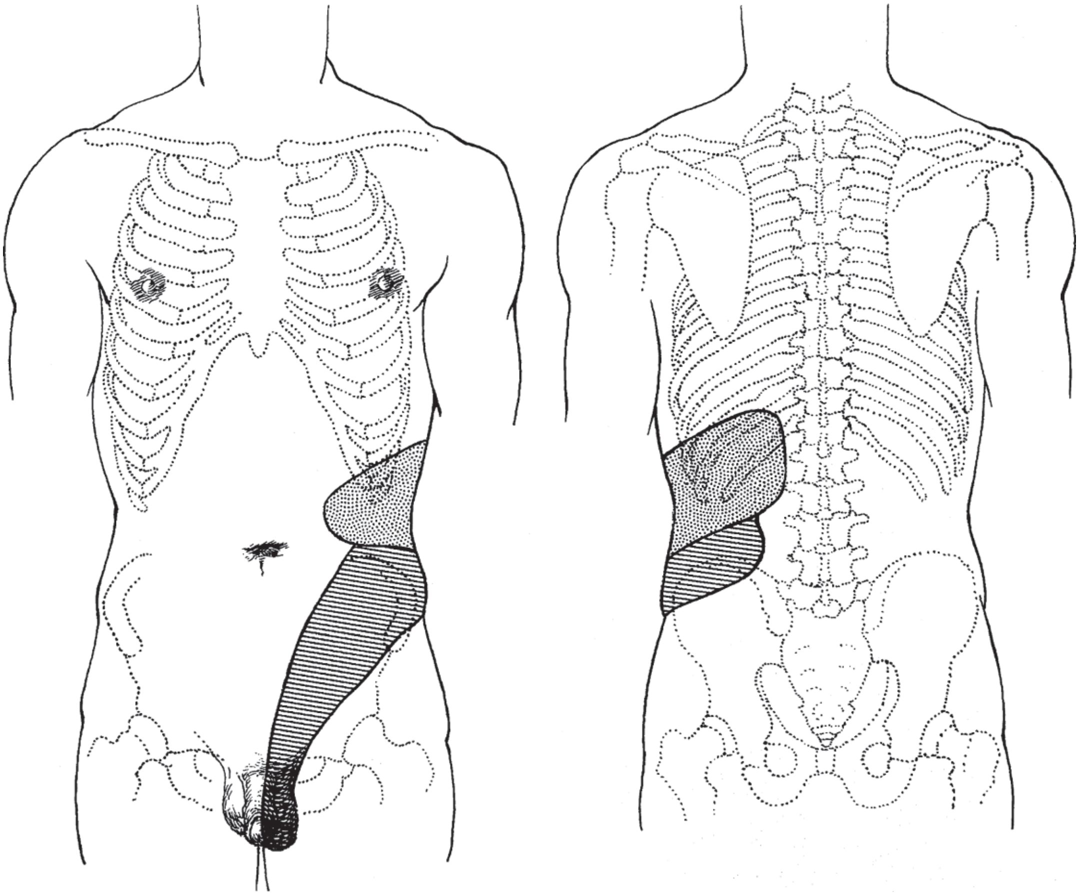
Local pain is felt in or near the involved organ. Thus, the pain from a diseased kidney (T10–T12, L1) is felt in the costovertebral angle and in the flank in the region of and below the 12th rib. Pain from an inflamed testicle is felt in the gonad itself.

Referred pain originates in a diseased organ but is felt at some distance from that organ. The ureteral colic (Figure 3–1) caused by a stone in the upper ureter may be associated with severe pain in the ipsilateral testicle; this is explained by the common innervation of these two structures (T11–T12). A stone in the lower ureter may cause pain referred to the scrotal wall; in this instance, the testis itself is not hyperesthetic. The burning pain with voiding that accompanies acute cystitis is felt in the distal urethra in females and in the glandular urethra in males (S2–S3).

Abnormalities of a urologic organ can also cause pain in any other organ (eg, gastrointestinal, gynecologic) that has a sensory nerve supply common to both (Figures 3–2 and 3–3).

▶ Kidney Pain (Figure 3–1)

Typical renal pain is felt as a dull and constant ache in the costovertebral angle just lateral to the sacrospinalis muscle and just below the 12th rib. This pain often spreads along the subcostal area toward the umbilicus or lower abdominal quadrant. It may be expected in the renal diseases that cause sudden distention of the renal capsule. Acute pyelonephritis (with its sudden edema) and acute ureteral obstruction (with its sudden renal back pressure) both cause this typical pain.



▲ **Figure 3–1.** Referred pain from kidney (dotted areas) and ureter (shaded areas).

It should be pointed out, however, that many urologic renal diseases are painless because their progression is so slow that sudden capsular distention does not occur. Such diseases include cancer, chronic pyelonephritis, staghorn calculus, tuberculosis, polycystic kidney, and hydronephrosis due to chronic ureteral obstruction.

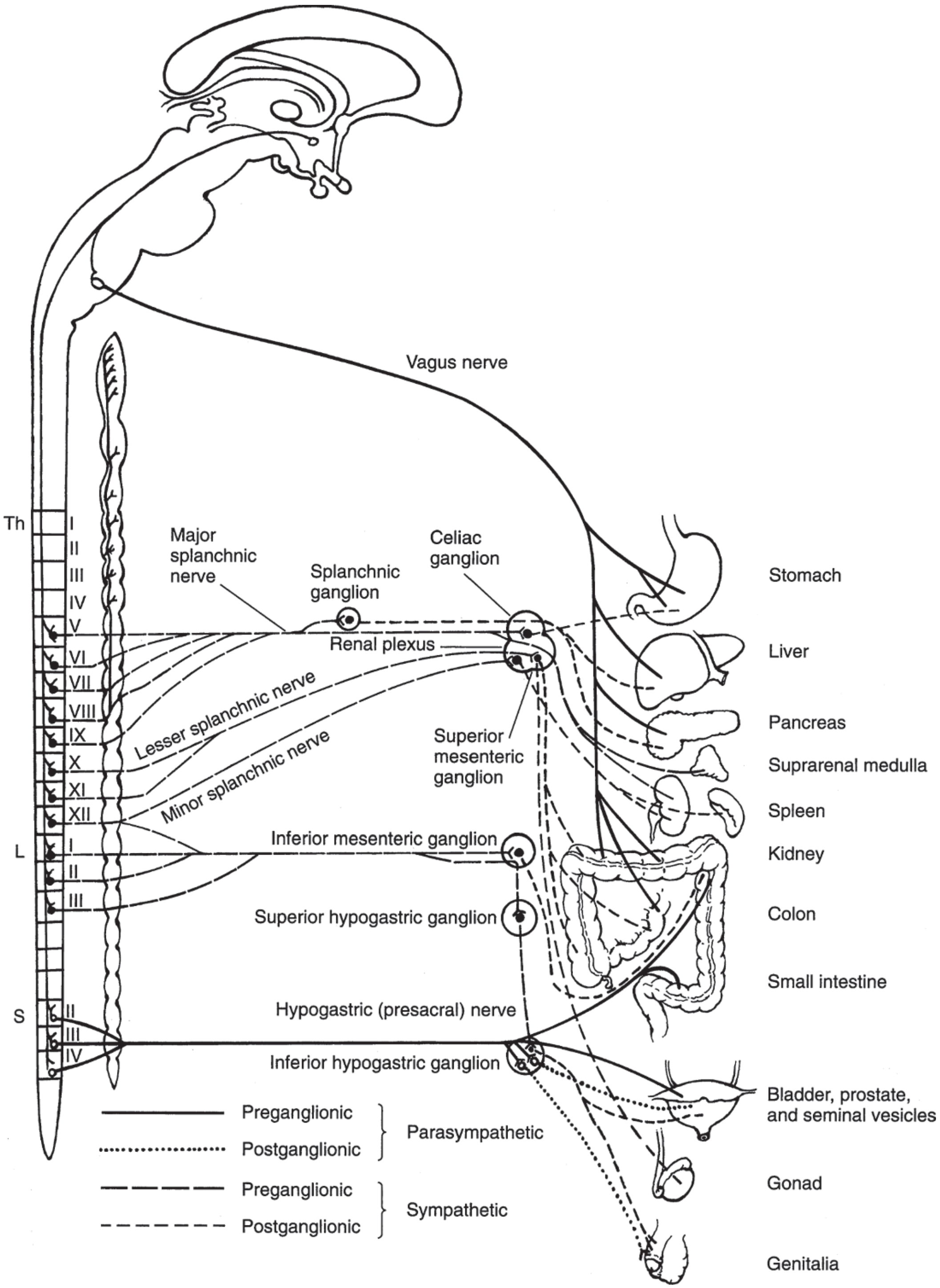
Ureteral Pain (Figure 3–1)

Ureteral pain is typically stimulated by acute obstruction (passage of a stone or a blood clot). In this instance, there is back pain from renal capsular distention combined with severe colicky pain (due to renal pelvic and ureteral muscle spasm) that radiates from the costovertebral angle down toward the lower anterior abdominal quadrant, along the course of the ureter. In men, it may also be felt in the bladder, scrotum, or testicle. In women, it may radiate into the vulva. The severity and colicky nature of this pain are caused by the hyperperistalsis and spasm of this smooth-muscle organ as it attempts to rid itself of a foreign body or to overcome obstruction.

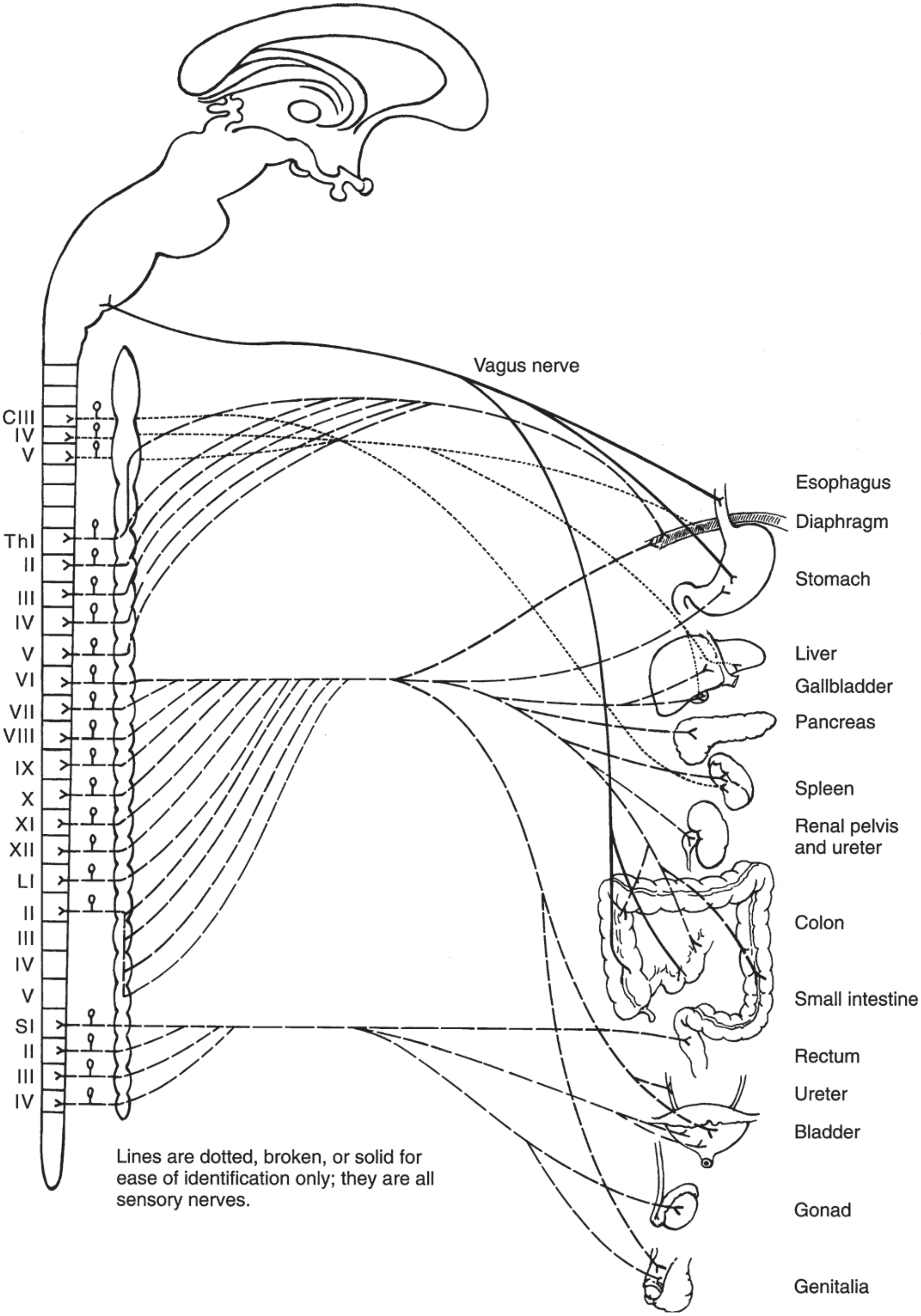
The physician may be able to judge the position of a ureteral stone by the history of pain and the site of referral. If the stone is lodged in the upper ureter, the pain radiates to the testicle, since the nerve supply of this organ is similar to those of the kidney and upper ureter (T11–T12). With stones in the midportion of the ureter on the right side, the pain is referred to McBurney's point and may therefore simulate appendicitis; on the left side, it may resemble diverticulitis or other diseases of the descending or sigmoid colon (T12, L1). As the stone approaches the bladder, inflammation and edema of the ureteral orifice ensue, and symptoms of vesical irritability such as urinary frequency and urgency may occur. It is important to realize, however, that in mild ureteral obstruction, as seen in the congenital stenoses, there is usually no pain, either renal or ureteral.

Vesical Pain

The overdistended bladder of the patient in acute urinary retention causes agonizing pain in the suprapubic area. Other



▲ **Figure 3–2.** Diagrammatic representation of autonomic nerve supply to gastrointestinal and genitourinary tracts.



Lines are dotted, broken, or solid for ease of identification only; they are all sensory nerves.

▲ **Figure 3–3.** Diagrammatic representation of sensory nerves of gastrointestinal and genitourinary tracts.

than this, however, constant suprapubic pain not related to the act of urination is rarely of urologic origin.

The patient in chronic urinary retention due to bladder neck obstruction or neurogenic bladder may experience little or no suprapubic discomfort even though the bladder reaches the level of the umbilicus.

The most common cause of bladder pain is infection; the pain is seldom felt over the bladder but is referred to the distal urethra and is related to the act of urination. Terminal dysuria may be a major complaint in severe cystitis. Pain related to urinary urgency and detrusor overactivity can result in bladder pain.

▶ Prostatic Pain

Direct pain from the prostate gland is not common. Occasionally, when the prostate is acutely inflamed, the patient may feel a vague discomfort or fullness in the perineal or rectal area (S2–S4). Lumbosacral backache is occasionally experienced as referred pain from the prostate but is not a common symptom of prostatitis. Inflammation of the gland may cause dysuria, frequency, and urgency.

▶ Testicular Pain

Testicular pain due to trauma, infection, or torsion of the spermatic cord is very severe and is felt locally, although there may be some radiation of the discomfort along the spermatic cord into the lower abdomen. Uninfected hydrocele, spermatocele, and tumor of the testis do not commonly cause pain. A varicocele may cause a dull ache in the testicle that is increased after heavy exercise. At times, the first symptom of an early indirect inguinal hernia may be testicular pain (referred). Pain from a stone in the upper ureter may be referred to the testicle.

▶ Epididymal Pain

Acute infection of the epididymis is the only painful disease of this organ and is quite common. The pain begins in the scrotum, and some degree of neighborhood inflammatory reaction involves the adjacent testis as well, further aggravating the discomfort. In the early stages of epididymitis, pain may first be felt in the groin or lower abdominal quadrant. (If on the right side, it may simulate appendicitis.) This may be a referred type of pain but can be secondary to associated inflammation of the vas deferens.

GASTROINTESTINAL SYMPTOMS OF UROLOGIC DISEASES

Whether renal or ureteral disease is painful or not, gastrointestinal symptoms are often present. The patient with acute pyelonephritis not only has localized back pain, symptoms of vesical irritability, chills, and fever but also experiences generalized abdominal pain and distention. A patient who is passing a stone down the ureter has typical renal and ureteral colic and, usually, hematuria and may experience severe nausea and vomiting as well as abdominal distention. However, the urinary symptoms so far overshadow the gastrointestinal symptoms that the latter are usually ignored. Inadvertent overdistention of the renal pelvis (eg, with opaque material in order to obtain adequate retrograde urograms) may cause the patient to become nauseated, vomit, and complain of cramplike pain in the abdomen. This clinical experiment demonstrates the renointestinal reflex, which may lead to confusing symptoms. In the very common “silent” urologic diseases, some degree of gastrointestinal symptomatology may be present, which could mislead the clinician into seeking the diagnosis in the intraperitoneal zone.

▶ Cause of the Mimicry

A. Renointestinal Reflexes

Renointestinal reflexes account for most of the confusion. They arise because of the common autonomic and sensory innervations of the two systems (Figures 3–2 and 3–3). Afferent stimuli from the renal capsule or musculature of the pelvis may, by reflex action, cause pylorospasm (symptoms of peptic ulcer) or other changes in tone of the smooth muscles of the enteric tract and its adnexa.

B. Organ Relationships

The right kidney is closely related to the hepatic flexure of the colon, the duodenum, head of the pancreas, the common bile duct, the liver, and the gallbladder (Figure 1–3). The left kidney lies just behind the splenic flexure of the colon and is closely related to the stomach, pancreas, and spleen. Inflammations or tumors in the retroperitoneum thus may extend into or displace intraperitoneal organs, causing them to produce symptoms.

The bladder is housed on top of the rectum. Conditions such as constipation, irritable bowel syndrome, and chronic diarrhea often occur simultaneously with voiding dysfunction. Frequently treating the gastrointestinal disease will improve voiding.

C. Peritoneal Irritation

The anterior surfaces of the kidneys are covered by peritoneum. Renal inflammation, therefore, causes peritoneal irritation, which can lead to muscle rigidity and rebound tenderness.

The symptoms arising from chronic renal disease (eg, noninfected hydronephrosis, staghorn calculus, cancer, chronic pyelonephritis) may be entirely gastrointestinal and may simulate in every way the syndromes of peptic ulcer, gallbladder disease, or appendicitis, or other, less specific gastrointestinal complaints. If a thorough survey of the gastrointestinal tract fails to demonstrate suspected disease processes, the physician should give every consideration to study of the urinary tract.

SYMPTOMS RELATED TO THE ACT OF URINATION

Many conditions cause symptoms of "cystitis." These include infections of the bladder, vesical inflammation due to chemical or x-radiation reactions, interstitial cystitis, prostatitis, mental illness (eg, depression and anxiety), torsion or rupture of an ovarian cyst, and foreign bodies in the bladder. Often, however, the patient with chronic cystitis notices no symptoms of vesical irritability. Irritating chemicals or soap on the urethral meatus may cause cystitis-like symptoms of dysuria, frequency, and urgency. This has been specifically noted in young girls taking frequent bubble baths.

Frequency

The normal capacity of the bladder is about 400 mL. Frequency may be caused by residual urine, which decreases the functional capacity of the organ. When the mucosa, submucosa, and even the muscularis become inflamed (eg, infection, foreign body, stones, tumor), the capacity of the bladder decreases sharply. This decrease is due to two factors: the pain resulting from even mild stretching of the bladder and the loss of bladder compliance resulting from inflammatory edema. When the bladder is normal, urination can be delayed if circumstances require it, but this is not so in acute cystitis. Once the diminished bladder capacity is reached, any further distention may be agonizing, and the patient may urinate involuntarily if voiding does not occur immediately. During very severe acute infections, the desire to urinate may be constant, and each voiding may produce only a few milliliters of urine. Day frequency without nocturia and acute or chronic frequency lasting only a few hours suggest nervous tension.

Diseases that cause fibrosis of the bladder are accompanied by frequency of urination. Examples of such diseases are tuberculosis, radiation cystitis, interstitial cystitis, and schistosomiasis. The presence of stones or foreign bodies causes vesical irritability, but secondary infection is almost always present. A very low or very high urine pH can irritate the bladder and cause frequency of urination. Alcohol, caffeine, carbonated beverages, citrus, spicy foods, and chocolate can be bladder irritants that cause frequency and pain in some people.

Nocturia

Nocturia may be a symptom of renal disease related to a decrease in the functioning renal parenchyma with loss of concentrating power. Nocturia can occur in the absence of disease in persons who drink excessive amounts of fluid in the late evening. Coffee and alcoholic beverages, because of their specific diuretic effects, often produce nocturia if consumed just before bedtime. In older people who are ambulatory, some fluid retention may develop secondary to mild heart failure or varicose veins. With recumbency at night, this fluid is mobilized, leading to nocturia in these patients.

Dysuria

Painful urination is usually related to acute inflammation of the bladder, urethra, or prostate. At times, the pain is described as "burning" on urination and is usually located in the distal urethra in men. In women the pain is usually localized to the urethra. The pain is present only with voiding and disappears soon after micturition is completed. More severe pain sometimes occurs in the bladder just at the end of voiding, suggesting that inflammation of the bladder is the likely cause. Pain also may be more marked at the beginning of or throughout the act of urination. Dysuria often is the first symptom suggesting urinary infection and is often associated with urinary frequency and urgency.

Enuresis

Strictly speaking, *enuresis* means bedwetting at night. It is physiologic during the first 2 or 3 years of life but becomes troublesome, particularly to parents, after that age. It may be functional or secondary to delayed neuromuscular maturation of the urethrovesical component, but it may present as a symptom of organic disease (eg, infection, distal urethral stenosis in girls, posterior urethral valves in boys, neurogenic bladder). If wetting occurs also during the daytime, however, or if there are other urinary symptoms, urologic investigation is essential. In adult life, enuresis may be replaced by nocturia for which no organic basis can be found.

Symptoms of Bladder Outlet Obstruction

A. Hesitancy

Hesitancy in initiating the urinary stream is one of the early symptoms of bladder outlet obstruction. As the degree of obstruction increases, hesitancy is prolonged and the patient often strains to force urine through the obstruction. Prostate obstruction and urethral stricture are common causes of this symptom.

B. Loss of Force and Decrease of Caliber of the Stream

Progressive loss of force and caliber of the urinary stream is noted as urethral resistance increases despite the generation of increased intravesical pressure. This can be evaluated by measuring urinary flow rates; in normal circumstances with a full bladder, a maximal flow of 20 mL/s should be achieved.

C. Terminal Dribbling

Terminal dribbling becomes more and more noticeable as obstruction progresses and is a most distressing symptom.

D. Urgency

A strong, sudden desire to urinate is caused by hyperactivity and irritability of the bladder, resulting from obstruction, inflammation, or neuropathic bladder disease. In most circumstances, the patient can control the sudden need to void temporarily, but loss of small amounts of urine may occur (urgency incontinence).

E. Acute Urinary Retention

Sudden inability to urinate may supervene. The patient experiences increasingly agonizing suprapubic pain associated with severe urgency and may dribble only small amounts of urine.

F. Chronic Urinary Retention

Chronic urinary retention may cause little discomfort to the patient even though there is great hesitancy in starting the stream and marked reduction of its force and caliber. Constant dribbling of urine (overflow incontinence) may be experienced; it may be likened to water pouring over a dam.

G. Intermittent Urinary Stream

Interruption may be abrupt and accompanied by severe pain radiating down the urethra. This type of reaction strongly suggests the complication of vesical calculus or prostate growth resembling a ball and valve.

H. Sense of Incomplete Emptying

The patient often feels that urine is still in the bladder even after urination has been completed.

I. Cystitis

Recurring episodes of acute cystitis suggest the presence of residual urine.

▶ Incontinence

There are many reasons for incontinence. The history often gives a clue to its cause. (See also Chapter 29.)

A. True Incontinence

The patient may lose urine without warning; this may be a constant or periodic symptom. The more obvious causes include previous radical prostatectomy, exstrophy of the bladder, epispadias, vesicovaginal fistula, and ectopic ureteral orifice. Injury to the urethral smooth-muscle sphincters may occur during prostatectomy or childbirth. Congenital or acquired neurogenic diseases may lead to dysfunction of the bladder and incontinence.

B. Stress Incontinence

When slight weakness of the sphincteric mechanisms is present, urine may be lost in association with physical strain (eg, coughing, laughing, rising from a chair). This is common in multiparous women who have weakened muscle support of the bladder neck and urethra and in men who have undergone radical prostatectomy. Occasionally, neuropathic bladder dysfunction can cause stress incontinence. The patient stays dry while lying in bed.

C. Urge Incontinence

Urgency may be so precipitate and severe that there is involuntary loss of urine. Urge incontinence frequently occurs with acute cystitis, particularly in women, since women seem to have relatively poor anatomic sphincters. Urge incontinence is a common symptom of an upper motor neuron lesion.

D. Overflow Incontinence

Paradoxic incontinence is loss of urine due to chronic urinary retention or secondary to a flaccid bladder. The intravesical pressure finally equals the urethral resistance; urine then constantly dribbles forth.

▶ Oliguria and Anuria

Oliguria and anuria may be caused by acute renal failure (due to shock or dehydration), fluid ion imbalance, or bilateral ureteral obstruction.

▶ Pneumaturia

The passage of gas in the urine strongly suggests a fistula between the urinary tract and the bowel. This occurs most commonly in the bladder or urethra but may be seen also in the ureter or renal pelvis. Carcinoma of the sigmoid colon, diverticulitis with abscess formation, regional enteritis, and trauma cause most vesical fistulas. Congenital anomalies account for most urethroenteric fistulas. Certain bacteria, by the process of fermentation, may liberate gas on rare occasions independent of a fistula.

▶ Cloudy Urine

Patients often complain of cloudy urine, but it is most often cloudy merely because it is alkaline; this causes precipitation of phosphate. Infection can also cause urine to be cloudy and malodorous. A properly performed urinalysis will reveal the cause of cloudiness.

▶ Chyluria

The passage of lymphatic fluid or chyle is noted by the patient as passage of milky white urine. This represents a lymphatic–urinary system fistula. Most often, the cause is obstruction of the renal lymphatics, which results in forniceal rupture and leakage. Filariasis, trauma, tuberculosis, and retroperitoneal tumors have caused this problem.

▶ Bloody Urine

Hematuria is a danger signal that cannot be ignored. Carcinoma of the kidney or bladder, calculi, and infection are a few of the conditions in which hematuria is typically demonstrable at the time of presentation. It is important to know whether urination is painful, whether the hematuria is associated with symptoms of vesical irritability, and whether blood is seen in all or only a portion of the urinary stream. The hemoglobinuria that occurs as a feature of the hemolytic syndromes may also cause the urine to be red.

A. Bloody Urine in Relation to Symptoms and Diseases

Hematuria associated with renal colic suggests a ureteral stone, although a clot from a bleeding renal tumor can cause the same type of pain.

Hematuria is commonly associated with nonspecific, tuberculous, or schistosomal infection of the bladder. The bleeding is often terminal (bladder neck or prostate), although it may be present throughout urination (vesical or upper tract). Stone in the bladder often causes hematuria, but infection is usually present, and there are symptoms of bladder neck obstruction, neurogenic bladder, or cystocele.

Dilated veins may develop at the bladder neck secondary to enlargement of the prostate. These may rupture when the patient strains to urinate, resulting in gross or microscopic hematuria.

Hematuria without other symptoms (silent hematuria) must be regarded as a symptom of tumor of the bladder or kidney until proved otherwise. It is usually intermittent; bleeding may not recur for months. Because the bleeding stops spontaneously, complacency must be condemned. Less common causes of silent hematuria are staghorn calculus, polycystic kidneys, benign prostatic hyperplasia, solitary renal cyst, sickle cell disease, and hydronephrosis. Painless bleeding is common with acute glomerulonephritis. Recurrent bleeding is occasionally seen in children suffering from focal glomerulitis. Joggers and people who engage in contact sports frequently develop transient proteinuria and gross or microscopic hematuria.

B. Time of Hematuria

Learning whether the hematuria is partial (initial, terminal) or total (present throughout urination) is often of help in identifying the site of bleeding. Initial hematuria suggests an anterior urethral lesion (eg, urethritis, stricture, meatal stenosis in young boys). Terminal hematuria usually arises from the posterior urethra, bladder neck, or trigone. Among the common causes are posterior urethritis and polyps and tumors of the vesical neck. Total hematuria has its source at or above the level of the bladder (eg, stone, tumor, tuberculosis, nephritis).

OTHER OBJECTIVE MANIFESTATIONS

▶ Urethral Discharge

Urethral discharge in men is one of the most common urologic complaints. The causative organism is usually *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. The discharge is often accompanied by local burning on urination or an itching sensation in the urethra (see Chapter 17).

▶ Skin Lesions of the External Genitalia

An ulceration of the glans penis or its shaft may represent syphilitic chancre, chancroid, herpes simplex, or squamous cell carcinoma. Venereal warts of the penis are common. (See Chapters 17 and 42.)

▶ Visible or Palpable Masses

The patient may notice a visible or palpable mass in the upper abdomen that may represent a renal tumor, hydronephrosis, or polycystic kidney. Enlarged lymph nodes in the neck may contain metastatic tumor from the prostate or testis. Lumps in the groin may represent spread of tumor of the penis or lymphadenitis from chancroid, syphilis, or lymphogranuloma venereum. Painless masses in the scrotal contents are common and include hydrocele, varicocele, spermatocele, chronic epididymitis, hernia, and testicular tumor.

▶ Edema

Edema of the legs may result from compression of the iliac veins by lymphatic metastases from prostatic cancer. Edema of the genitalia suggests filariasis, chronic ascites, or lymphatic blockage from radiotherapy for pelvic malignancies.

▶ Bloody Ejaculation

Inflammation of the prostate or seminal vesicles can cause hematospermia.

▶ Gynecomastia

Often idiopathic, gynecomastia is common in elderly men, particularly those taking estrogens for control of prostatic cancer. It is also seen in association with choriocarcinoma and interstitial cell and Sertoli cell tumors of the testis. Certain endocrinologic diseases, such as Klinefelter syndrome, may also cause gynecomastia.

SEXUAL DYSFUNCTION IN MEN AND WOMEN

Sexual wellness and dysfunction in men and women is influenced by multiple physiologic and psychologic domains. Dysfunction in hormonal, neural, and vascular pathways can all lead to sexual dysfunction. Sexuality is strongly influenced by one's surrounding culture; one's family and societal and religious beliefs influence sex life practices. Sexual wellness changes with aging, one's health status, and personal experience.

All evaluations should start with a thorough history and physical examination. The urologist should learn about the nature of the concern as well as aggravating or relieving factors. For example, sexual dysfunction may be situational; the patient may be able to masturbate and may awaken with morning erections, but during partnered intimacy, erectile dysfunction may occur. The urologist must learn about past medical and surgical history as well as medications.

Common sexual dysfunction among men include hypoactive sexual desire disorder (HSDD) premature ejaculation, erectile dysfunction, and anorgasmia. Common female sexual dysfunction includes HSDD, dysfunction in arousal, orgasm, and sexual pain disorders such as vaginismus.

BIBLIOGRAPHY

Abul F et al: The acute scrotum: A review of 40 cases. Med Princ Pract 2005;14(3):177.

Ahmed M et al: Ureteric bupivicaine infusion for loin pain haematuria syndrome. Ann Roy Coll Surg Engl 2010;92(2):139–141.

Ahn JH et al: Workup and management of traumatic hematuria. Emerg Med Clin North Am 1998;16:145.

Andreoli SP: Renal manifestations of systemic diseases. Semin Nephrol 1998;18:270.

Anonymous: Blood in the urine: What does it mean for your health? Harv Mens Health Watch 2010;15(3):5–8.

Beni-Israel T et al: Clinical predictors for testicular torsion as seen in the pediatric ED. Am J Emerg Med 2010;28(7):786–789.

Breyer BN, McAninch JW: Management of recalcitrant bladder neck contracture after radical prostatectomy for prostate cancer. Endoscopic and open surgery. J Urol 2011;185(2):390–391.

Catalano O et al: Real-time, contrast-enhanced sonographic imaging in emergency radiology. Radiol Med (Torino) 2004;108(5–6):454.

Chhor V et al: Misleading abdominal pain following extracorporeal renal lithotripsy. Urol Int 2009;83(2):246–248.

Ciftci AO et al: Clinical predictors for differential diagnosis of acute scrotum. Eur J Pediatr Surg 2004;14:333.

Crawford ED: Management of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: The central role of the patient risk profile. BJU Int 2005;95(Suppl 4):1.

Eisner BH et al: Ureteral stone location at emergency room presentation with colic. J Urol 2009;182(1):165–168.

Elstad EA et al: Beyond incontinence: The stigma of other urinary symptoms. J Adv Nurs 2010;66(11):2460–2470.

Glassberg KI: Normal and abnormal development of the kidney: A clinician's interpretation of current knowledge. J Urol 2002; 167:2339.

Green E, Ali Z: Flank pain and haematuria. BMJ 2009;339:b5443.

Heinberg LJ et al: Psychological factors in pelvic/urogenital pain: The influence of site of pain versus sex. Pain 2004;108(1–2):88.

Ho CH et al: Predictive factors for ureteral double-J-stent-related symptoms: A prospective, multivariate analysis. J Formos Med Assoc 2010;109(11):848–856.

Hollenbeck BK et al: Delays in diagnosis and bladder cancer mortality. Cancer 2010;116(22):5235–5242.

Hori S et al: Long-term outcome of epididymectomy for the management of chronic epididymal pain. J Urol 2009;182(4):1407–1412.

Kanematsu A et al: Objective patterning of uroflowmetry curves in children with daytime and nighttime wetting. J Urol 2010; 184(4 Suppl):1674–1679.

Kaye JD, Palmer LS: Characterization and management of voiding dysfunction in children with attention deficit hyperactivity disorder. Urology 2010;76(1):220–224.

Kershen RT et al: Blood flow, pressure and compliance in the male human bladder. J Urol 2002;168:121.

Khadra MH et al: A prospective analysis of 1930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000; 163:524.

Kumar P et al: Clinical management of chronic testicular pain. Urol Int 2010;84(2):125–131.

Kumar A et al: A prospective randomized comparison between early (<48 hours of onset of colicky pain) versus delayed shockwave lithotripsy for symptomatic upper ureteral calculi: A single center experience. J Endourol 2010;24(12):2059–2066.

Kurowski K: The women with dysuria. Am Fam Physician 1998; 57(9):2155.

Lee YS et al: Most bothersome symptom and symptom specific goal achievement in patients with benign prostatic obstruction: A prospective open label study. J Urol 2011;185(3):1003–1009.

Lutz MC et al: Cross-sectional associations of urogenital pain and sexual function in a community based cohort of older men: Olmsted County, Minnesota. J Urol 2005;174:624.

Manger JP et al: Use of renal ultrasound to detect hydronephrosis after ureteroscopy. J Endourol 2009;23(9):1399–1402.

Mevcha A et al: Diagnosing urological disorders in ageing men. Practitioner 2010;254(1726):2–3, 25–26, 28–29.

Nappi PR et al: Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). Maturitas 2016;94:87–91.

Navanimitkul N, Lojanapiwat B: Efficacy of tamsulosin 0.4 mg/day in relieving double-J stent-related symptoms: A randomized controlled study. J Int Med Res 2010;38(4):1436–1441.

Nickel JC et al: Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: A prospective multicenter clinical trial. J Urol 2001; 165:1539.

Nickel JC et al: The patient with chronic epididymitis: Characterization of an enigmatic syndrome. J Urol 2002;167:1701.

Nitti VW et al: Lower urinary tract symptoms in young men: Videourodynamic findings and correlation with noninvasive measures. J Urol 2002;168:135.

Oelke M et al: Nocturia: state of the art and critical analysis of current assessment and treatment strategies. World J Urol 2014; 32(5):1109–1117.

Pabon-Ramos W et al: Excretory urography: Trends in clinical use and diagnostic yield. Abdom Imaging 2010;35(5):607–611.

Paryavi E et al: Acute exertional lumbar paraspinal compartment syndrome. Spine (PhilaDelphia, 1976) 2010;35(25):E1529–E1533.

Payne C: Urodynamics for the evaluation of painful bladder syndrome/interstitial cystitis. J Urol 2010;184(1):15–16.

Persaud AC et al: Pediatric urolithiasis: Clinical predictors in the emergency department. Pediatrics 2009;124(3):888–894.

Quddus MB, Mahmud SM: Testicular torsion: A diagnosis not to be missed. J Pak Med Assoc 2011;61(4):391–392.

Roehrborn CG: Male lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). Med Clin North Am 2011; 95(1):87–100.

Sea J et al: Review of exercise and the risk of benign prostatic hyperplasia. Phys Sportsmed 2009;37(4):75–83.

Steinberg PL et al: A standardized pain management protocol improves timeliness of analgesia among emergency department patients with renal colic. Qual Manag Health Care 2011; 20(1):30–36.

Sunela KL et al: Changes in symptoms of renal cell carcinoma over four decades. BJU Int 2010;106(5):649–653.

Swinn MJ et al: The cause and natural history of isolated urinary retention in young women. J Urol 2002;167:151.

Swithinbank LV et al: The natural history of daytime urinary incontinence in children: A large British cohort. Acta Paediatr 2010; 99(7):1031–1036.

Wampler SM, Llanes M: Common scrotal and testicular problems. Prim Care 2010;37(3):613–626, x.

Weiss JP, Blaivas JG: Nocturia. J Urol 2000;163:5.

Wik L et al: Exertional paraspinal muscle rhabdomyolysis and compartment syndrome: A cause of back pain not to be missed. Clin Rheumatol 2010;29(7):803–805.

Wong LM et al: Creation and validation of a visual macroscopic hematuria scale for optimal communication and an objective hematuria index. J Urol 2010;184(1):231–236.

Wu JN et al: Palliative care in urology. Surg Clin North Am 2011; 91(2):429–444, x.

Physical Examination of the Genitourinary Tract

4

Maxwell V. Meng, MD, MPH; & Emil A. Tanagho, MD

A careful history and assessment of symptoms will suggest whether a complete or limited examination is indicated and will also help direct the appropriate selection of subsequent diagnostic studies.

EXAMINATION OF THE KIDNEYS

Inspection

A mass that is visible in the upper abdominal area may be difficult to palpate if soft, as with hydronephrosis. Fullness in the costovertebral angle (CVA) may be consistent with cancer or perinephric infection. The presence and persistence of indentations in the skin from lying on wrinkled sheets suggest edema of the skin secondary to perinephric abscess.

Palpation

The kidneys lie rather high under the diaphragm and lower ribs and are therefore well protected from injury. Because of the position of the liver, the right kidney is lower than the left. The kidneys are difficult to palpate in men because of (1) resistance from abdominal muscle tone and (2) more fixed position than in women, moving only slightly with change of posture or respiration. The lower part of the right kidney can sometimes be felt, particularly in thin patients, but the left kidney rarely can be felt unless it is enlarged or displaced.

The most successful method of renal palpation is carried out with the patient lying in the supine position on a hard surface (Figure 4–1). The kidney is lifted by one hand in the CVA. On deep inspiration, the kidney moves downward; the other hand is pushed firmly and deeply beneath the costal margin so as to trap the kidney. When successful, the anterior hand can palpate the size, shape, and consistency of the organ as it slips back into its normal position.

Alternatively, the kidney may be palpated with the examiner standing behind the seated patient. At other times, if the patient is lying on one side, the uppermost kidney drops downward and medially, making it more accessible to palpation. Perlman and Williams (1976) described an effective method of identifying renal anomalies in newborns. The fingers are placed in the CVA, with the thumb anterior and performing the palpation.

An enlarged renal mass suggests compensatory hypertrophy (if the other kidney is absent or atrophic), hydronephrosis, tumor, cyst, or polycystic disease. However, a mass in this area may also represent a retroperitoneal tumor, spleen, lesion of the bowel (eg, tumor, abscess), lesion of the gallbladder, or pancreatic cyst. Tumors may have the consistency of normal tissue or be nodular, while hydronephrosis may be either firm or soft. Polycystic kidneys are usually nodular and firm.

An acutely infected kidney is tender, but the presence of marked muscle spasm may make this difficult to elicit. In addition, this sign may not always be helpful since the normal kidney is also often tender.

Although renal pain may be diffusely felt in the back, tenderness is usually well localized, just lateral to the sacrospinalis muscle and below the 12th rib (ie, CVA). Symptoms may be elicited by palpation or sharp percussion over the CVA.

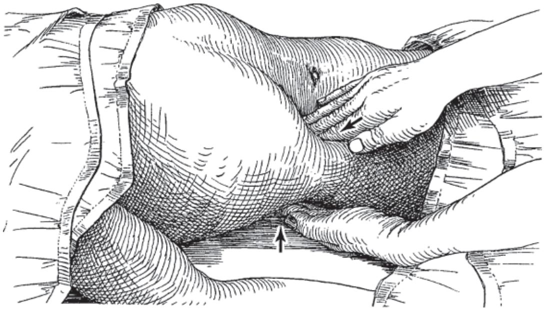
Percussion

At times, an enlarged kidney cannot be felt, particularly if it is soft as in some cases of hydronephrosis. However, such masses may be outlined by both anterior and posterior percussion, and this part of the examination should not be omitted.

Percussion is of special value in outlining an enlarging mass (progressive hemorrhage) in the flank following renal trauma, when tenderness and muscle spasm prevent palpation.

Transillumination

Transillumination may prove helpful in children younger than 1 year who present with a suprapubic or flank mass.



▲ **Figure 4–1.** Method of palpation of the kidney. The posterior hand lifts the kidney upward. The anterior hand feels for the kidney. The patient then takes a deep breath; this causes the kidney to descend. As the patient inhales, the fingers of the anterior hand are plunged inward at the costal margin. If the kidney is mobile or enlarged, it can be felt between the two hands.

A dark room is required along with a flashlight with an opaque flange protruding beyond the lens. The flashlight is applied at a right angle to the abdomen. The fiberoptic light cord, used to illuminate various optical instruments, is an excellent source of cold light. A distended bladder or cystic mass will transilluminate; a solid mass will not. Flank masses may be assessed by applying the light posteriorly.

Differentiation of Renal and Radicular Pain

Radicular pain is commonly felt in the costovertebral and subcostal areas. It may also spread along the course of the ureter and is the most common cause of so-called kidney pain. Every patient who complains of flank pain should be examined for evidence of nerve root irritation. Frequent causes are poor posture (scoliosis, kyphosis), arthritic changes in the costovertebral or costotransverse joints, impingement of a rib spur on a subcostal nerve, hypertrophy of costovertebral ligaments pressing on a nerve, and intervertebral disk disease (Smith and Raney, 1976). Radicular pain may be noted as an aftermath of a flank incision where a rib is dislocated, causing impingement of costal nerve on the edge of a ligament. Pain experienced during the preeruptive phase of herpes zoster involving any of the segments between T11 and L2 may simulate pain of renal origin.

Radiculitis usually causes hyperesthesia of the area of skin served by the irritated peripheral nerve. This hypersensitivity can be elicited by means of the pinwheel or grasping and pinching both skin and fat of the abdomen and flanks. Pressure exerted by the thumb over the costovertebral joints reveals local tenderness at the point of emergence of the involved nerve.

Auscultation

Auscultation of the costovertebral areas and upper abdominal quadrants may reveal a systolic bruit, often associated with stenosis or aneurysm of the renal artery. Bruits over the femoral arteries may be found in association with Leriche syndrome, which may be a cause of impotence.

EXAMINATION OF THE BLADDER

The bladder cannot be felt unless it is moderately distended. In adults, it contains at least 150 mL of urine if it can be percussed. In acute or chronic urinary retention, the bladder may reach or even rise above the umbilicus, when its outline may be seen and usually felt. In chronic retention, the bladder may be difficult to palpate because of the flabby bladder wall, in which case percussion is of value.

In male infants or young boys, palpation of a hard mass deep in the center of the pelvis is compatible with a thickened, hypertrophied bladder secondary to obstruction caused by posterior urethral valves.

A sliding inguinal hernia containing some bladder wall can be diagnosed by compression of the scrotal mass when the bladder is full, leading to additional distension.

A few instances have been reported where marked edema of the legs has developed secondary to compression of the iliac vessels by a distended bladder. Bimanual (abdominorectal or abdominovaginal) palpation may reveal the extent of a vesical tumor; to be successful, it should be done under anesthesia.

EXAMINATION OF THE EXTERNAL MALE GENITALIA

Penis

A. Inspection

If the patient has not been circumcised, the foreskin should be retracted. This may reveal tumor or balanitis as the cause of foul discharge. If retraction is not possible because of phimosis, surgical correction (a dorsal slit or circumcision) is indicated.

The observation of a poor urinary stream is significant; in newborns, neurogenic bladder or the presence of posterior urethral valves should be considered, whereas in men such a finding suggests urethral stricture or prostatic obstruction.

The scars of healed syphilis may be an important clue. An active ulcer requires bacteriologic or pathologic study (eg, syphilitic chancre, epithelioma). Superficial ulcers or vesicles are compatible with herpes simplex and often interpreted by the patient as a serious sexually transmitted disease (eg, syphilis). Venereal warts may be observed.

Meatal stenosis is a common cause of bloody spotting in male infants. On occasion, it may be of such degree as to cause advanced bilateral hydronephrosis.

The position of the meatus should be noted. It may be located proximal to the tip of the glans on either the dorsal (epispadias) or the ventral (hypospadias) surface. In either instance, there is apt to be abnormal curvature (chordee) of the penis in the direction of the displaced meatus.

Micropenis or macropenis may be noted during examination of the penis. In the neonate, the presence of hypospadias and bilateral undescended testes should suggest the possibility of an intersex condition.

B. Palpation

Palpation of the dorsal surface of the shaft may reveal a fibrous plaque involving the tunica albuginea covering of the corpora cavernosa, typical of Peyronie's disease. Tender areas of induration felt along the urethra may signify periurethritis secondary to urethral stricture.

C. Urethral Discharge

Urethral discharge is the most common complaint referable to the male sex organ. Gonococcal pus is usually profuse, thick, and yellow or gray-brown. Nongonorrheal discharges may be similar in appearance but are often thin, mucoid, and scant. Although gonorrhea must be ruled out as the cause of urethral discharge, a significant percentage of cases are found to be caused by chlamydiae. Patients with urethral discharge should also be examined for other sexually transmitted diseases since multiple infection is not uncommon.

Bloody discharge suggests the possibility of a foreign body in the urethra, urethral stricture, or tumor.

Urethral discharge must always be sought before the patient is asked to void.

▶ Scrotum

Angioneurotic edema and infections and inflammation of the skin of the scrotum are not common. Small sebaceous cysts are occasionally seen, while malignant tumors are rare. The scrotum is bifid when midscrotal or perineal hypospadias is present.

Elephantiasis of the scrotum is caused by obstruction to lymphatic drainage and endemic in the tropics due to filariasis. Genital lymphedema may also result from radical resection of the lymph nodes of the inguinal and femoral areas, in which case the skin of the penis is involved. Small hemangiomas of the skin are common and may bleed spontaneously.

Scrotal ultrasound is a helpful adjunct in evaluating the scrotal contents.

▶ Testis

The testes should be carefully palpated with the fingers of both hands. A hard area in the testis proper must be regarded as a malignant tumor until proven otherwise. Transillumination of scrotal masses should be done routinely. With the patient in a dark room, a flashlight or fiberoptic light is placed against the scrotal sac posteriorly. A hydrocele will cause the intrascrotal mass to glow red; conversely, light is not transmitted through a solid tumor. Tumors are often smooth but may be nodular, and the testes may seem abnormally heavy. A testis replaced by tumor or damaged by gumma is insensitive to pressure, and the usual sickening sensation is absent. About 10% of tumors are associated with a secondary hydrocele that may require aspiration before definitive palpation can be performed.

The testis may be absent from the scrotum, and this may be transient (physiologic retractile testis) or true cryptorchidism. Palpation of the groins may reveal the presence of the organ.

The atrophic testis (postoperative orchiopexy, mumps orchitis, or torsion of the spermatic cord) may be flabby and at times hypersensitive but is usually firm and hyposensitive. Although spermatogenesis may be absent, androgen function is occasionally maintained.

▶ Epididymis

The epididymis is sometimes rather closely attached to the posterior surface of the testis, and at other times, it is quite free of it. The epididymis should be carefully palpated for size and induration, which implies infection since primary tumors are exceedingly rare.

In the acute stage of epididymitis, the testis and epididymis are indistinguishable by palpation; the testicle and epididymis may be adherent to the scrotum, which is usually red and exquisitely tender. With few exceptions, the infecting organism is *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Escherichia coli*.

Chronic painless induration suggests tuberculosis or schistosomiasis, although nonspecific chronic epididymitis is also possible. Other signs of genitourinary tuberculosis include sterile pyuria, thickened seminal vesicle, nodular prostate, and "beading" of the vas deferens.

▶ Spermatic Cord and Vas Deferens

A swelling in the spermatic cord may be cystic (eg, hydrocele or hernia) or solid (eg, connective-tissue tumor), although the latter is rare. Lipoma in the investing fascia of the cord may simulate a hernia. Diffuse swelling and induration of the cord are seen with filarial funiculitis.

Careful palpation of the vas deferens may reveal thickening (eg, chronic infection), fusiform enlargements ("beading" caused by tuberculosis), or even absence of the vas. The latter finding is of importance in infertile males and may be associated with cystic fibrosis or ipsilateral Wolffian duct abnormality (eg, renal agenesis).

When a male patient stands, a mass of dilated veins (varicocele) may be noted behind and above the testis. The degree of dilatation decreases with recumbency and can be increased by the Valsalva maneuver. The major potential sequela of varicocele is infertility (see Chapter 43).

▶ Testicular Tunics and Adnexa

Hydroceles are usually cystic but on occasion so tense that they simulate solid tumors; transillumination confirms the diagnosis. The fluid may accumulate secondary to nonspecific acute or tuberculous epididymitis, trauma, or tumor of the testis. The latter is a distinct possibility if the hydrocele appears spontaneously between the ages of 18 and 35 years. It should be aspirated to permit careful palpation of underlying structures or further characterized with ultrasonography.

Hydroceles usually surround the testis completely. Cystic masses that are separate from but in the region of the upper pole of the testis are typically spermatoceles. Aspiration reveals the typical thin, milky fluid, which contains sperm.

EXAMINATION OF THE FEMALE GENITALIA

Vaginal Examination

Diseases of the female genital tract may secondarily involve the urinary organs, making a thorough gynecologic examination essential, which should be performed by the male physician in the presence of a female nurse or health professional. Commonly associated conditions include urethrocystitis secondary to urethral diverticulitis or cervicitis, pyelonephritis during pregnancy, and ureteral obstruction from metastatic nodes or direct extension from cervical cancer.

A. Inspection

In newborns and children, the vaginal vestibule should be inspected for a single opening (common urogenital sinus), labial fusion, split clitoris and lack of fusion of the anterior fourchette (epispadias), or hypertrophied clitoris and scrotalization of the labia majora (adrenogenital syndrome).

The urinary meatus may reveal a reddened, tender, friable lesion (urethral caruncle) or a reddened, everted posterior lip often seen with senile urethritis and vaginitis. Biopsy is indicated if a malignant tumor cannot be ruled out. The diagnosis of senile vaginitis and urethritis is established by staining a smear of the vaginal epithelium with Lugol's solution. Cells lacking glycogen (hypoestrogenism) do not take up the stain, whereas normal cells do.

Multiple painful small ulcers or blister-like lesions may be noted, usually representing herpes virus type 2 infection, which may have serious sequelae.

Smears and cultures of urethral or vaginal discharge should be made. Gonococci are relatively easy to identify; culture of chlamydiae requires techniques that are seldom available to the physician.

The presence of skenitis and bartholinitis may reveal the source of persistent urethritis or cystitis. The condition of the vaginal wall should be observed. Urethrocele and cystocele, often found with stress incontinence, may be associated with residual urine and lead to persistent infection of the bladder. A bulge in the anterior vaginal wall may represent a urethral diverticulum. The cervix should be inspected for cancer or infection. Taking biopsy specimens or making Papanicolaou smears may be indicated.

B. Palpation

At times, the urethra, base of the bladder, and lower ureters may be tender on palpation, but little can be deduced from this finding. Induration of the urethra or trigonal area, or a mass involving either, may be a clue to an existing tumor. A soft mass could be a urethral diverticulum, and pressure may cause pus to extrude from the urethra. A stone in the lower ureter may be palpable. Evidence of enlargement of the uterus (eg, pregnancy, myoma) or diseases or inflammations of the colon or adnexa may afford a clue to the cause of urinary symptoms (eg, compression of ureter by ovarian tumor, endometriosis, or diverticulitis of the sigmoid colon adherent to the bladder).

Carcinoma of the cervix may invade the base of the bladder, causing vesical irritability or hematuria; metastases to iliac lymph nodes may compress the ureters.

Rectal examination may provide further information and is the obvious route of examination in children and virgins.

RECTAL EXAMINATION IN MALES

Sphincter and Lower Rectum

The estimation of sphincter tone is of importance. Laxity of the muscle suggests similar changes in the urinary sphincter and detrusor and the possibility of neurogenic disease; the same is true for a spastic anal sphincter. In addition to the digital prostatic examination, the examiner should palpate the entire lower rectum to rule out stenosis, internal hemorrhoids, cryptitis, rectal fistulae, mucosal polyps, and rectal cancer. Testing perianal sensation is mandatory.

Prostate

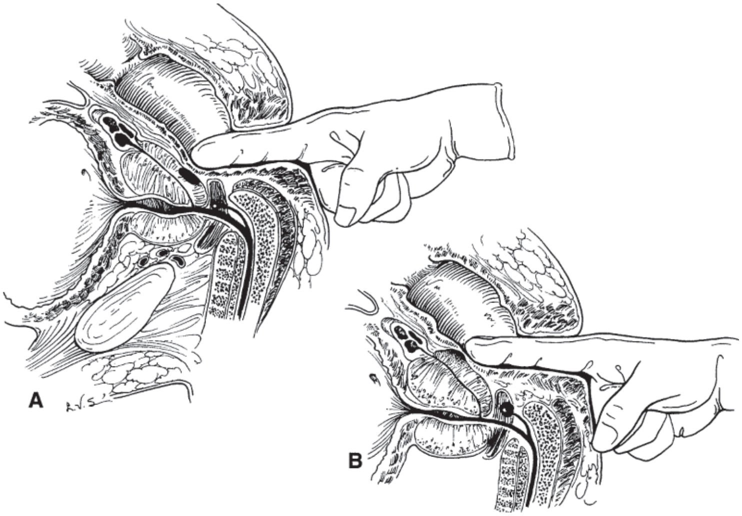
A specimen of urine for routine analysis should be collected before the rectal examination. This is of importance, since prostatic massage or even palpation at times forces prostatic secretion into the posterior urethra. If this secretion contains pus, a specimen of voided urine after the rectal examination will be contaminated.

A. Size

The average prostate is about 4 cm in both length and width. As the gland enlarges, the lateral sulci become relatively deeper and the median furrow becomes obliterated. The clinical importance of prostatic hyperplasia is measured by the severity of symptoms and the amount of residual urine rather than by the size of the gland on palpation. The prostate may be of normal size and consistency on examination in a patient with acute urinary retention or severe obstructive urinary complaints.

B. Consistency

Normally, the consistency of the gland is similar to the consistency of the contracted thenar eminence of the thumb



▲ **Figure 4–2.** Differential diagnosis of prostatic nodules. ***A:*** Inflammatory area is raised above the surface of the gland; induration decreases gradually at its periphery. ***B:*** Cancerous nodule is not raised; there is an abrupt change in consistency at its edges.

(with the thumb completely opposed to the little finger) and is rather rubbery. It may be mushy if congested (due to lack of intercourse or chronic infection with impaired drainage), indurated (due to chronic infection with or without calculi), or stony hard (due to advanced carcinoma).

The difficulty lies in differentiating firm areas in the prostate: fibrosis from nonspecific infection, granulomatous prostatitis, nodularity from tuberculosis, or firm areas due to prostatic calculi or early cancer. Generally, nodules caused by infection are raised above the surface of the gland. At their edges, the induration gradually fades to the normal softness of surrounding tissue. Conversely, the suspicious lesion in cases of prostate cancer is seldom raised; rather, it is hard and has a sharp edge (ie, there is an abrupt change in consistency on the same plane). It tends to arise in the lateral sulcus (Figure 4–2).

Even the most experienced clinician can have trouble differentiating cancer from other conditions. The serum prostate–specific antigen (PSA) level can be helpful if elevated and is currently the most common method of diagnosing prostate cancer (clinical stage T1c). Transrectal ultrasound-guided biopsy of the prostate can be diagnostic. Recent evidence suggests that rectal examination after radical prostatectomy is unnecessary when PSA is undetectable, since no case of locally recurrent cancer was identified in the absence of an elevated PSA.

C. Mobility

The mobility of the gland varies. Occasionally, it has great mobility while at other times, very little. With advanced carcinoma, it is fixed because of local extension through the capsule. In adults, the prostate should be routinely massaged, and its secretion should be examined microscopically. However, prostatic massage should be avoided in the presence of an acute urethral discharge, acute prostatitis, or acute prostatocystitis; in men near the stage of complete urinary retention (because it may precipitate complete retention); or in men suffering from obvious cancer of the gland.

D. Massage and Prostatic Smear

Copious amounts of secretion may be obtained from some prostate glands and little or none from others. The amount obtained depends to some extent on the vigor with which the massage is carried out. If no secretion is obtained, the patient should be asked to void even a few drops of urine, as these will contain adequate secretion for examination. Microscopic examination of the secretion is done under low-power magnification. Normal secretion contains numerous lecithin bodies, which are refractile like red blood cells but much smaller. Only an occasional white cell is present. A few epithelial cells and, rarely, corpora amylacea are seen. Sperm may be present, but its absence is of no significance.

The presence of large numbers or clumps of leukocytes suggests prostatitis. Stained smears are usually impractical because it is difficult to fix the material on the slide; even when fixation and staining are successful, pyogenic bacteria are rarely found. Acid-fast organisms can often be found by appropriate staining methods.

On occasion, it may be necessary to obtain cultures of prostatic secretion in order to demonstrate nonspecific organisms, tubercle bacilli, gonococci, or chlamydiae. After thorough cleansing of the glans and emptying of the bladder to mechanically cleanse the urethra, the prostate is massaged. Drops of secretion are collected in a sterile tube of appropriate culture medium.

Seminal Vesicles

Palpation of the seminal vesicles should be attempted. The vesicles are situated under the base of the bladder and diverge from below upward (Figure 1–8). Normal seminal vesicles are usually impalpable but may feel cystic when they are overdistended. In the presence of chronic infection (particularly tuberculosis or schistosomiasis) or in association with advanced carcinoma of the prostate, they may be indurated. Stripping of the seminal vesicles should be done in association with prostatic massage, for the vesicles are usually infected when prostatitis is present. Primary tumors of the vesicles are very rare. A cystic mass may rarely be felt over the prostate or just above it. This probably represents a cyst of the Müllerian duct or the utricle; the latter is occasionally associated with severe hypospadias.

Lymph Nodes

It should be remembered that generalized lymphadenopathy usually occurs early in human immunodeficiency syndrome (see Chapter 16).

A. Inguinal and Subinguinal Lymph Nodes

With inflammatory lesions of the skin of the penis and scrotum or vulva, the inguinal and subinguinal lymph nodes may be involved. Such diseases include chancroid, syphilitic chancre, lymphogranuloma venereum, and on occasion, gonorrhea.

Malignant tumors (squamous cell carcinoma) involving the penis, glans, scrotal skin, or distal urethra in women metastasize to the inguinal and subinguinal nodes. Testicular tumors do not spread to these nodes unless they have invaded the scrotal skin or if the patient has previously undergone orchidopexy.

B. Other Lymph Nodes

Tumors of the testis and prostate may involve the left supraclavicular nodes (Virchow's or Troisier's node). Tumors of the bladder and prostate typically metastasize to the internal iliac, external iliac, and preaortic nodes, although they are rarely so large as to be palpable. Upper abdominal masses near the midline in a young man should suggest metastases from cancer of the testis; the primary growth may be minute and hidden in the substance of what appears to be a normal testicle.

NEUROLOGIC EXAMINATION

A careful neurologic survey may uncover sensory or motor impairment that account for residual urine or incontinence. Since the bladder and sphincter are innervated by the second to the fourth sacral segments, information can be gained by testing anal sphincter tone, evaluating sensation of the perianal skin, and testing Achilles tendon and bulbocavernosus reflexes. The bulbocavernosus reflex is elicited by placing a finger in the rectum and squeezing the glans penis or clitoris, or by jerking on an indwelling Foley catheter. The normal reflex involves contraction of the anal sphincter and bulbocavernosus muscles in response to these maneuvers.

It is wise, particularly in children, to seek a dimple over the lumbosacral area. One should palpate the sacrum to ensure that it is present and normally formed. Sacral agenesis or partial development is compatible with deficits of S2–S4. If findings seem abnormal, x-ray examination is indicated.

BIBLIOGRAPHY

Examination of the Kidneys

Lowe LH et al: Pediatric renal masses: Wilms tumor and beyond. Radiographics 2000;20:1585. [PMID: 11112813]

Mofenson HC, Greensher J: Transillumination of the abdomen in infants. Am J Dis Child 1968;115:428. [PMID: 5642347]

Perlman M, Williams J: Detection of renal anomalies by abdominal palpation in newborn infants. Br Med J 1976;3:347. [PMID: 947418]

Smith DR, Raney FL Jr: Radiculitis distress as a mimic of renal pain. J Urol 1976;116:269. [PMID: 957487]

External Genitalia in Males

Bemelmans BL et al: Penile sensory disorders in erectile dysfunction: Results of a comprehensive neuro-urophysiological diagnostic evaluation in 123 patients. J Urol 1991;146:777. [PMID: 1875492]

Galejs LE: Diagnosis and treatment of the acute scrotum. Am Fam Physician 1999;59:817. [PMID: 10068706]

Hanson P et al: Sacral reflex latencies in tethered cord syndrome. Am J Phys Med Rehabil 1993;72:39. [PMID: 8431266]

Horstman WG: Scrotal imaging. Urol Clin North Am 1997;24:653. [PMID: 9275983]

Lavoipierre AM: Ultrasound of the prostate and testicles. World J Surg 2000;24:198. [PMID: 10633147]

Kolettis PN et al: Clinical and genetic features of patients with congenital unilateral absence of the vas deferens. Urology 2002;60:1073. [PMID: 12475673]

Lavoisier P et al: Bulbocavernosus reflex: Its validity as a diagnostic test of neurogenic impotence. J Urol 1989;141:311. [PMID: 2913351]

Leissner J et al: The undescended testis: Considerations and impact on fertility. BJU Int 1999;83:885. [PMID: 10368225]

Marcozzi D, Suner S: The nontraumatic, acute scrotum. Emerg Med Clin North Am 2001;19:547. [PMID: 11554275]

Sherrard J, Barlow D: Gonorrhoea in men: Clinical and diagnostic aspects. Genitourin Med 1996;72:422. [PMID: 9038638]

Wolf CK et al: The undescended testicle. Compr Ther 2001;27:11. [PMID: 11280851]

External Genitalia in Females

Edmonds DK: Congenital malformations of the genital tract. Obstet Gynecol Clin North Am 2000;27:49. [PMID: 10693182]

Redman JF: Techniques of genital examination and bladder catheterization in female children. Urol Clin North Am 1990;17:1. [PMID: 2305501]

Prostate

Carroll P et al: Prostate-specific antigen best practice policy—part II: Prostate cancer staging and post-treatment follow-up. Urology 2001;57:225. [PMID: 11182325]

Grossfeld GD, Coakley FV: Benign prostatic hyperplasia: Clinical overview and value of diagnostic imaging. Radiol Clin North Am 2000;38:31. [PMID: 10664665]

Lummus WE, Thompson I: Prostatitis. Emerg Med Clin North Am 2001;19:691. [PMID: 11554282]

Nickel JC: The Pre and Post Massage Test (PPMT): A simple screen for prostatitis. Tech Urol 1997;3:38. [PMID: 9170224]

Obek C et al: Comparison of digital rectal examination and biopsy results with the radical prostatectomy specimen. J Urol 1999; 161:494. [PMID: 9915434]

Pound CR et al: Digital rectal examination and imaging studies are unnecessary in men with undetectable prostate specific antigen following radical prostatectomy. J Urol 1999;162:1337. [PMID: 10492192]

Neurologic Examination

Cardenas DD et al: Lower urinary changes over time in suprasacral spinal cord injury. Paraplegia 1995;33:326. [PMID: 7644258]

Vodusek DB: Electromyogram, evoked sensory and motor potentials in neurourology. Neurophysiol Clin 1997;27:204. [PMID: 9260161]

This page intentionally left blank

5

Urologic Laboratory Examination

Anobel Y. Odisho, MD, MPH; Sima P. Porten, MD, MPH;
& Kirsten L. Greene, MD, MS*

INTRODUCTION

Examination of specimens of urine, blood, and genitourinary secretions or exudates commonly directs the subsequent urologic workup and frequently establishes a diagnosis. Over 27 million outpatient visits per year are for common urologic diagnoses (Litwin and Saigal, 2012), and it is important for the physician to have a broad knowledge of the laboratory methods available to test appropriate specimens. Judicious use of such tests permits rapid, accurate, and cost-effective determination of the probable diagnosis and directs the management of patients with urologic disease.

EXAMINATION OF URINE

Urinalysis is one of the most important and useful urologic tests available, yet all too often, the necessary details are neglected and significant information is overlooked or misinterpreted (Simerville et al, 2005). Reasons for inadequate urinalyses include (1) improper collection, (2) failure to examine the specimen immediately, (3) incomplete examination (eg, few laboratories perform a microscopic analysis unless it is specifically requested by the provider), (4) inexperience of the examiner, and (5) inadequate appreciation of the significance of the findings. There is no role for routine urinalysis for patient screening, and it should be reserved when clinically indicated, such as in patients with urinary tract symptoms or signs (Davis et al, 2012; Anonymous, 2012; Hagan et al, 2018). Studies indicate that macroscopic analysis (dipstick) has limited predictive value for urinary tract infection due to low sensitivity (44–77%) and specificity (66–87%), but it may be useful in specific situations, discussed below (Hessdoerfer et al, 2011; Little et al, 2009, 2010).

▶ Urine Collection

A. Timing of Collection

It is best to examine urine that has been properly obtained in the office or lab. First morning voided specimens are helpful for qualitative protein testing in patients with renal disease due to diabetes or hypertension, or in identifying benign orthostatic proteinuria (Witte et al, 2009). Urine specimens that are obtained immediately after the patient has eaten or that have been left standing for a few hours become alkaline and thus may contain lysed red cells, disintegrated casts, or rapidly multiplying bacteria; therefore, a freshly voided specimen obtained a few hours after the patient has eaten and examined within 1 hour of voiding is most reliable. The patient's state of hydration may alter the concentration of urinary constituents. Timed urine collections (24-hour) may be required for definitive assessment of renal function or proteinuria. Examination of a urine specimen collected sequentially during voiding in several containers may help to identify the site of origin of hematuria or urinary tract infection.

B. Method of Collection

Proper collection of the specimen is particularly important as it impacts interpretability of results. The specimen should be obtained before a genital or rectal examination in order to prevent contamination from the introitus or expressed prostatic secretions. Urine obtained from a condom or chronic catheter, or intestinal conduit drainage bag is *not* a proper specimen for urinalysis. For dipstick analysis, urine should be at room temperature; all other specimens should be refrigerated.

1. Adults—It is usually simple to collect a clean-voided midstream urine sample from adults. Routine instructions may be printed on a sheet given to the patient or placed on the lavatory wall. In men, the foreskin should be retracted prior to voiding. The glans and meatus in men or perineum with spreading of labia in women can be cleansed with a castile soap towelette, although in a small study this was not shown to have a significant impact on contamination rates (Lifshitz and Kramer, 2000). The patient then passes the first part of the stream (15–30 mL) without collection, and collects the next or midstream portion (approximately 50–100 mL) in a sterile specimen container, which is immediately capped. A portion of the specimen is prepared for both macroscopic and microscopic examination, and the rest is saved in the sterile container for subsequent culture if necessary. With this midstream clean-catch method, the likelihood that the specimen will be contaminated by meatal or urethral secretions is markedly decreased, although not completely eliminated. In adult males, it is rarely necessary to collect urine by catheterization unless urinary retention is present.

---

*Originally written by Karl J. Kreder Jr, MD, and Richard D. Williams, MD.

2. Children—Urine for analysis, other than bacterial cultures, can be obtained from males or females by covering the cleansed urethral meatus with a plastic bag. A urine specimen for culture may require catheterization or suprapubic needle aspiration in children too young to void spontaneously. Suprapubic needle aspiration is performed as follows: (1) cleanse the suprapubic area by sponging with alcohol, (2) with a small amount of local anesthetic, raise an intradermal wheal on the midline 1–2 cm above the pubis (the bladder lies just above the pubis in young children), (3) attach a 10-mL syringe to a 22-gauge needle, and (4) insert the needle perpendicularly through the abdominal wheal into the bladder wall, maintaining gentle suction with the syringe so that urine will be aspirated as soon as the bladder is entered.

▶ Macroscopic Examination

A. Color and Appearance

Urine can be discolored by drugs; phenazopyridine (Pyridium) will turn the urine orange, rifampin will turn it yellow-orange, nitrofurantoin will turn it brown, and levodopa and metronidazole will turn it reddish-brown. Red urine does not always signify hematuria. A red discoloration unassociated with intact erythrocytes in the urine can result from betacyanin excretion after beet ingestion, phenolphthalein in laxatives, ingestion of vegetable dyes, concentrated urate excretion, myoglobinuria due to rhabdomyolysis, or hemoglobinuria following hemolysis. In addition, *Serratia marcescens* bacteria can cause the "red diaper" syndrome. However, whenever red urine is seen, hematuria must be ruled out by microscopic analysis. Cloudy urine is commonly thought to represent pyuria, but more often the cloudiness is due to large amounts of amorphous phosphates, which disappear with the addition of acid, or urates, which dissolve with the use of alkali. The odor of urine is rarely clinically significant.

B. Specific Gravity

The specific gravity of urine (normal: 1.003–1.030) reflects urine osmolality and is important for diagnostic purposes. A low specific gravity (<1.010) reflects hydration (real or perceived by the body), and a high specific gravity (>1.020) reflects dehydration. In patients with significant intracranial trauma, it may be low owing to a lack of antidiuretic hormone (vasopressin), that of patients with primary diabetes insipidus is <1.010 even after overnight dehydration, that of patients with extensive acute renal tubular damage is consistently 1.010 (similar to the specific gravity of plasma), and a low specific gravity can be an early sign of renal damage from conditions such as sickle cell anemia. Urine specific gravity is the simplest time-honored test for evaluating hydration in postoperative patients. The specific gravity of urine may affect the results of other urine tests; in dilute urine, a pregnancy test may be falsely negative; in concentrated urine, protein may be falsely positive on dipstrips yet unconfirmed on quantitative tests. The specific gravity of urine may be falsely elevated by the presence of glucose, protein, artificial plasma expanders, or intravenous contrast agents.

Alkaline pH may falsely lower the result (0.005 per pH unit >7.0).

C. Chemical Tests

Chemically impregnated reagent strips are accurate and have simplified routine urinalysis greatly. However, they must be monitored routinely by appropriate standardized quality-control reagents. The dipstrips are reliable only when not outdated and when used with *room-temperature* urine.

1. pH—The normal pH of urine is between 4.5 and 8 and is important in a few specific clinical situations. Patients with uric acid stones rarely have a urinary pH >6.5 as uric acid is soluble in alkaline urine. Patients with calcium stones, nephrocalcinosis, or both may have renal tubular acidosis and will be unable to acidify urine pH <6.0. With urinary tract infections caused by urea-splitting organisms (eg, *Proteus*, *Pseudomonas,* and *Klebsiella* species), the urinary pH tends to be >7.0. It should be reemphasized that urine obtained within 2 hours of a large meal or left standing at room temperature for several hours tends to be alkaline.

2. Protein—Dipstrips containing bromphenol blue can be used to determine the presence of >10 mg/dL protein in urine, which subsequently requires quantitative protein testing for confirmation. The dipstrip measures primarily albumin and is not sensitive to Bence Jones proteins (immunoglobulins). Concentrated urine may give a false-positive result, as will urine containing numerous leukocytes or vaginal secretions replete with epithelial cells. Orthostatic proteinuria can be demonstrated by detecting elevated protein levels in a urine specimen obtained after the patient has been in the upright position for several hours, whereas normal levels are found before ambulation. Prolonged fever and excessive physical exertion are also common causes of transient proteinuria. Persistently elevated protein levels in the urine (>150 mg/24 hours) may indicate significant disease. Therefore, specific quantitative protein tests, electrophoretic studies of the urine, or both may be required to determine the specific type of protein that is present.

3. Glucose—The glucose oxidase–peroxidase tests used in dipstrips are quite accurate and specific for urinary glucose. False-positive results may be obtained when patients have ingested large doses of aspirin, ascorbic acid, or cephalosporins. However, most patients with a positive reading have diabetes mellitus.

4. Hemoglobin—The dipstrip test for hemoglobin is not specific for erythrocytes and should be used only to *screen* for hematuria, with microscopic analysis of the urinary sediment used for confirmation. If a patient has a positive dipstick but a negative microscopic evaluation, the microscopic exam should be repeated 3 times for verification (Davis et al, 2012). American Urological Association guidelines recognize hematuria as three or more red blood cells per high-power field (≥3 RBC/hpf) (Davis et al, 2012). Free hemoglobin or myoglobin in the urine may give a positive reading; ascorbic acid in the urine can inhibit the dipstrip reaction and give a false-negative result. Note that dilute urine (<1.008) will lyse erythrocytes and thus provide a positive dipstrip reading for hemoglobin but no visible erythrocytes on microscopic analysis.

5. Bacteria and leukocytes—Test strips to determine the number of bacteria (nitrite) or leukocytes (leukocyte esterase) as predictors of bacteriuria are as specific but not particularly sensitive as microscopic evaluation. The nitrite reductase test depends on the conversion of nitrate to nitrite. Many of the bacteria responsible for urinary tract infections, particularly enterobacteria, can reduce nitrate to nitrite and are, therefore, detectable by this test. When the nitrite test is positive, it suggests the presence of >10,000 organisms per milliliter; however, several factors can lead to false-negative results. The nitrite test is positive only for coagulase-splitting bacteria, and thus, when used alone, it is only 40–60% accurate. Urine must be in the bladder long enough before sampling for the reduction of nitrate to occur (>4 hours); therefore, this test is most likely to be positive when first-voided morning urine is tested. A false-negative nitrite study may occur in patients taking rifampin, phenazopyridine, or ascorbic acid. Test strips left open to air for even one week can react with nitrates in the air and lead to a false-positive result (Gallagher et al, 1990).

The leukocyte esterase test is a widely used chemical test that depends on the presence of esterase in granulocytic leukocytes. The leukocyte esterase test is an indication of pyuria and will remain positive even after the leukocytes have degenerated. The test accurately identifies patients with 10–12 leukocytes per high-power field in a centrifuged specimen. Although this test is a good indicator of pyuria, it does not detect bacteriuria. Therefore, it is often combined with the nitrite test to detect both bacteriuria and inflammation to maximize the chances of predicting urinary tract infection. Used together, the two tests are as predictive as the microscopic analysis but not as accurate as a urine culture.

Microscopic Examination

Early-morning urine is the best specimen if it can be examined within a few minutes of collection. In most cases, the sediment can be prepared as follows: (1) centrifuge a 10-mL specimen at 2000 rpm for 5 minutes; (2) decant the supernatant; (3) resuspend the sediment in the remaining 1 mL of urine by tapping the tube gently against a countertop; and (4) place one drop of the mixture on a microscope slide, cover with a coverslip, and examine first under low-power (10×) lens and then under a high-power (40×) lens. For maximal contrast of the elements in the sediment, the microscope diaphragm should be nearly closed to prevent overillumination. Significant elements (particularly bacteria) are more easily seen if the slide is stained with methylene blue, but staining is not essential. Figure 5–1 shows typical findings in the urinary sediment.

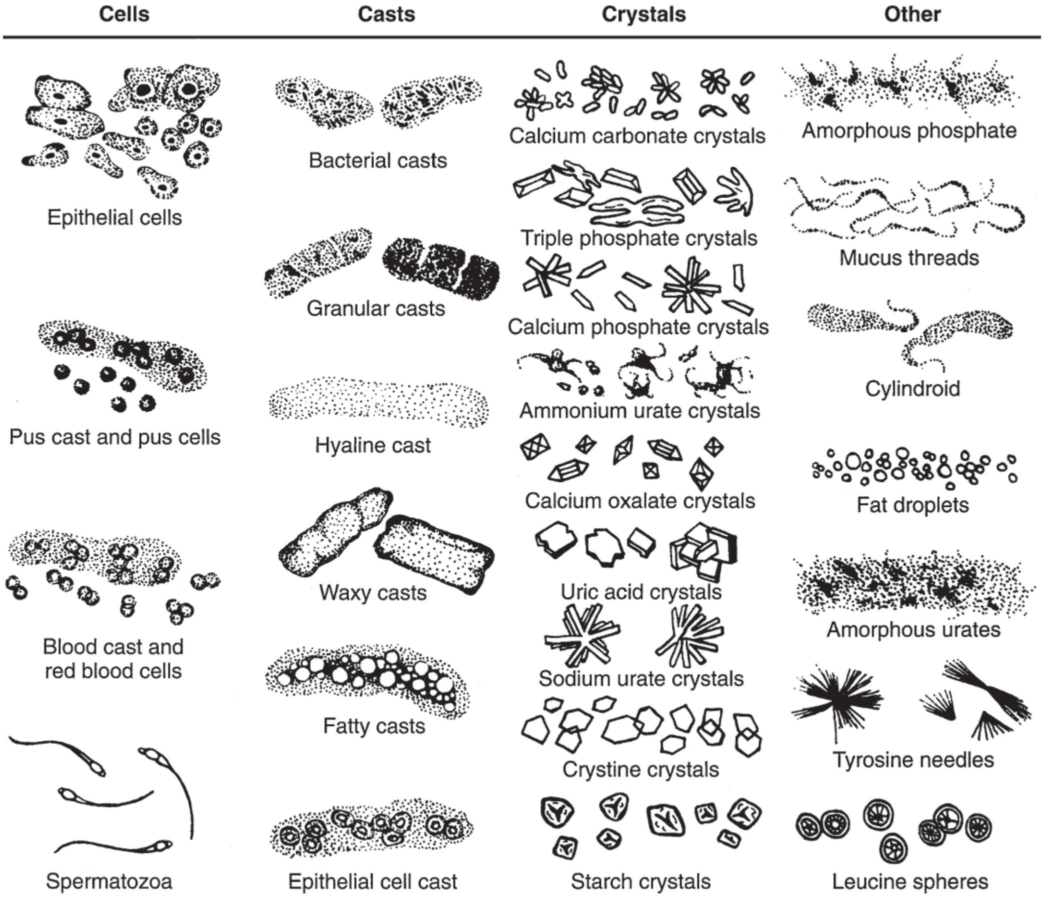
A. Interpretation

1. Bacteria—The significance of bacteria in the urinary sediment is discussed in the section "Bacteriuria."

2. Leukocytes—Just as the presence of bacteria in the sediment is not an absolute indication of infection, neither is the finding of pyuria. In the sediment from clean-voided midstream specimens, a finding of more than five leukocytes per high-power field is generally considered abnormal (pyuria). If the patient has symptoms of a urinary tract infection as well as pyuria and bacteriuria, one is justified in making a diagnosis of infection and initiating empiric therapy. However, in female patients with symptoms of urinary tract infection, 60% of those with pyuria will have no bacterial growth from bladder urine obtained by catheterization or suprapubic aspiration emphasizing the need for confirmation by bacterial cultures.

Renal tuberculosis can cause "sterile" acid pyuria and should be considered in any patient with persistent pyuria and negative results on routine bacterial cultures. Specific fluorescent staining of the urinary sediment for acid-fast bacteria can be diagnostic; however, results will be positive from the sediment of spot specimens in only approximately 50% of patients with renal tuberculosis, whereas they are positive in the sediment of 24-hour specimens in 70–80% of such cases. *Mycobacterium smegmatis*, a commensal organism, may be present in the urine (particularly in uncircumcised men) and can give false-positive results on acid-fast stains.

Urolithiasis can also cause pyuria. In patients with persistent pyuria, the physician should consider obtaining at



▲ **Figure 5–1.** Microscopic examination of urine sediment.

least a plain x-ray of the abdomen and possibly a computed tomography (CT) urogram to determine whether urolithiasis is present. Similarly, a retained foreign body such as a self-induced bladder object or a forgotten internal ureteral stent can cause pyuria. An x-ray of the abdomen should reveal the offender.

3. Erythrocytes—The presence of even a few erythrocytes in the urine is abnormal and requires further investigation. Infrequent causes of hematuria include strenuous exercise (long-distance running), vaginal bleeding, and inflammation of organs near or directly adjoining the urinary tract, such as diverticulitis or appendicitis. Hematuria associated with cystitis or urethritis generally clears after treatment. Persistent hematuria (≥3 RBC/hpf) in an otherwise asymptomatic patient, after other benign etiologies are ruled out, is an indication for further urologic evaluation (Davis et al, 2012). Studies indicate that approximately 12% of patients with gross hematuria will be diagnosed with bladder cancer, but this depends on underlying patient risk factors such as age and smoking status (Khadra et al, 2018).

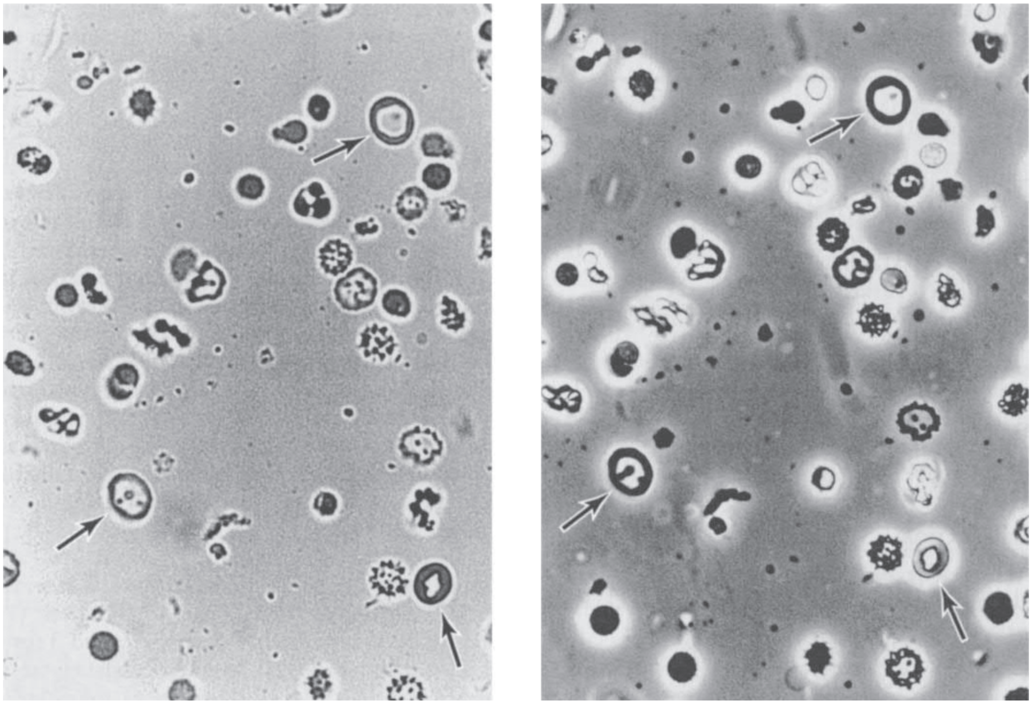
In patients with microscopic hematuria, a three-container method for collection of urine can provide information on the site of origin of erythrocytes. Give the patient three containers, labeled 1, 2, and 3 (or initial, mid, and final). Instruct the patient to urinate and to collect the initial portion of the urine stream (10–15 mL) in the first container, the middle portion (30–40 mL) in the second, and the final portion (5–10 mL) in the third. Using methods described previously, centrifuge the three specimens individually, prepare slides of the urinary sediment (with or without staining), and examine the slides microscopically. If erythrocytes predominate in the initial portion of the specimen, they are usually from the anterior urethra; those in the final portion are generally from the bladder neck or posterior urethra; and the presence of equal numbers of erythrocytes in all three containers usually indicates a source above the bladder neck (bladder, ureters, or kidneys). It is important to collect the urine before physical examination (particularly before rectal examination in men) to avoid misleading results.

The three-container test may not be necessary in patients with gross hematuria, since patients (men in particular) can usually tell the physician which portion of the stream contains the darkest urine (ie, the most erythrocytes). Dysmorphic erythrocytes are highly indicative of active glomerular disease (Figure 5–2). This dysmorphism is thought to be a result of extreme changes in osmolality and the high concentration of urinary chemical constituents affecting erythrocytes during passage through the kidney tubules.

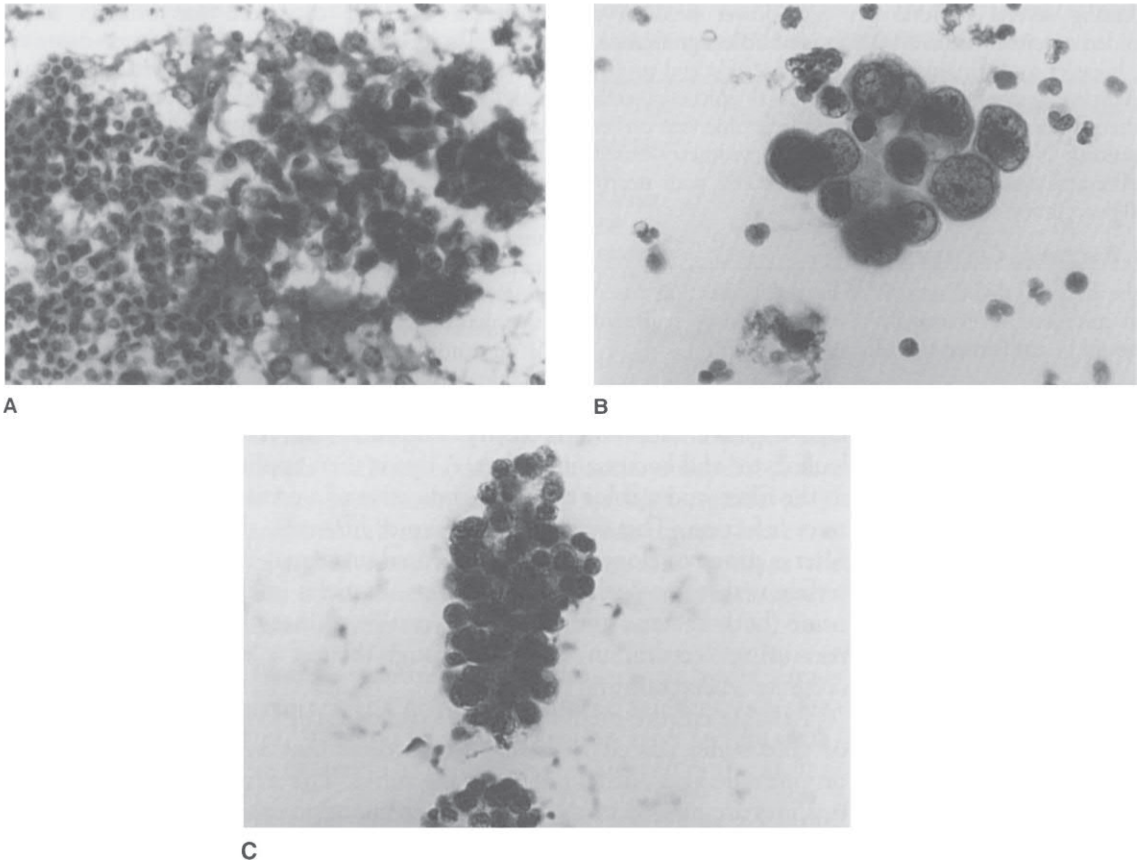
4. Epithelial cells—Squamous epithelial cells in the urinary sediment indicate contamination of the specimen from the distal urethra in males and from the introitus in females; no other significance should be placed on them. It is not uncommon to find transitional epithelial cells in the normal urinary sediment; however, if they are present in large numbers or clumps and are abnormal histologically (including large nuclei, multiple nucleoli, and an increased ratio of nucleus to cytoplasm), they may be indicative of a malignant process affecting the urothelium (Figure 5–3).

5. Casts—Casts are formed in the distal tubules and collecting ducts and are not typically seen in normal urinary sediment and therefore commonly signify intrinsic renal disease. Although *leukocyte casts* have been considered suggestive of pyelonephritis, they are not an absolute indicator and should not be used as the sole criterion for diagnosis. Leukocyte casts must be distinguished from *epithelial cell casts*, because the latter have little significance when present in small numbers. The distinction can be made easily if a small amount of acetic acid is added under the coverslip to enhance nuclear detail (note that casts tend to congregate near the edges of the coverslip). In renal transplant recipients, an increase in the number of epithelial cells or casts from the renal tubules may be an early indicator of acute graft rejection.

Erythrocyte casts are pathognomonic of underlying glomerulonephritis or vasculitis. Hyaline casts are comprised of mucoproteins congealed in the tubules. They are not significant when present in small numbers but may represent pyelonephritis or chronic renal disease in large numbers. Hyaline casts are commonly seen in urine specimens taken after exercise and in concentrated or highly acidic urine specimens. Casts are rarely seen in alkaline urine and are therefore rarely present in urine specimens that have been left standing or in specimens from patients unable to acidify. Granular casts most commonly represent disintegrated



▲ **Figure 5–2.** ***Left:*** Dysmorphic erythrocytes in urine (*arrows*), viewed under light microscopy (magnification 400×). ***Right:*** Dysmorphic erythrocytes in urine (identical field), viewed under phase-contrast microscopy. (Reproduced with permission from Stamey TA, Kindrachuk RW: Urinary Sediment and Urinalysis: *A Practical Guide for the Health Science Professional.* Philadelphia, PA: WB Saunders; 1985.)



▲ **Figure 5–3.** Papanicolaou-stained bladder cytology specimens. ***A:*** Normal cells (left) and malignant cells (right). ***B:*** High-power view of malignant cells. ***C:*** Papillary cluster of malignant cells. (Used with permission from Larry Kluskens, MD, Cytopathology Laboratory, University of Iowa.)

epithelial cells, leukocytes, or protein; they usually indicate intrinsic renal tubular disease.

6. Other findings—The finding of crystals in urine can be helpful in some instances, but the mere presence of crystals does not indicate disease. Crystals form in normal urine below room temperature. Cystine, leucine, tyrosine, cholesterol, bilirubin, hematoidin, and sulfonamide crystals are abnormal findings of varying importance. Several types of crystals that may be found on microscopic examination of urinary sediment are shown in Figure 5–1. High concentrations of protease inhibitors in the urine, such as indinavir, for treatment of human immunodeficiency virus (HIV), can lead to phrase inhibitor crystal formation in urine (Izzedine et al, 2014). The characteristic crystals are flat, rectangular plates, often in a fan or starburst pattern. The presence of trichomonads or yeast cells in the smear of sediment from a properly obtained urine specimen establishes a diagnosis.

▶ Bacteriuria

A. Microscopic Examination

A presumptive diagnosis of bacterial infection may be based on the results of microscopic examination of the urinary sediment. If several bacteria per high-power field are found in a urine specimen obtained by suprapubic aspiration or catheterization in a woman or in a properly obtained clean-voided midstream specimen from a man, a provisional diagnosis of bacterial infection can be made and empiric treatment started. Finding several bacteria per high-power field in a voided specimen from a woman is of little significance. The findings should be confirmed by bacterial culture.

B. Bacterial Cultures

The presumptive diagnosis of bacterial infection based on microscopic examination of the urinary sediment should be confirmed by culture. Cultures can be used to estimate the number of bacteria in the urine (quantitative cultures), to identify the exact organism present, and to assess which drugs will be effective in treating the infection. Cultures are particularly important in patients with recurrent or persistent infections, renal insufficiency, or drug allergies.

The number of bacteria present in the urine (colony count) is influenced by the method used to collect the urine specimen, the patient's hydration status, and whether the patient has been taking antimicrobial drugs. The concept that urinary tract infection is present only when the urine specimen contains 10^5 or more bacteria per milliliter is not an absolute rule; a lower count does not exclude the possibility of an infection, particularly in a symptomatic patient (Kunin et al, 2018). Cultures with growth of multiple organisms usually signify contamination. The presence of a few organisms in a specimen with a low specific gravity is more significant than the same finding in a specimen with a high specific gravity because the former is more dilute.

Identifying the drugs to which the bacteria are susceptible can be critical, particularly in severe or recurrent infection. Gram stains can provide rapid information, and empiric treatment can be initiated in accordance with guideline recommendations and hospital antibiograms. However, in patients with recurrent infections, septicemia, renal insufficiency, diabetes mellitus, or suspected enterococcal, *Proteus*, or *Pseudomonas* infections, it is important to determine the antibiotic sensitivity of the organism and the drug concentration necessary for efficacious treatment.

1. Cultures for tuberculosis—A microscopic examination (fluorescent stain) that shows acid-fast bacilli can give a presumptive diagnosis of urinary tuberculosis. The rapidity of recovering mycobacteria in culture depends somewhat on the patient's bacillary load. Thus, if the smear is highly positive (3–4+), cultures would become positive in 1–2 weeks. At that time, a DNA culture probe can be done for tuberculosis. It should be noted that the probe cannot distinguish between tuberculosis and patients treated with bacillus Calmette-Guérin (BCG); if the patient had not received BCG treatment, then *Mycobacterium tuberculosis* infection is likely. The total time from receipt of the specimen to presumptive diagnosis is typically about 2 weeks. Susceptibility tests, if positive for tuberculosis, would require another week.

Other Urine Tests

Many other tests of urine can be helpful in determining the presence of urologic disease.

A. Urothelial Cancer Tests

The evaluation of voided or bladder wash (barbotage) urine for bladder urothelial cancer cells has been quite successful for high-grade tumors and carcinoma in situ with high specificity (81–100%) but low sensitivity (38–51%) (Konety, 2018; Mowatt et al, 2010). Low-grade tumors less commonly shed abnormal cells, and cytology is relatively insensitive in this setting, but has a high positive predictive value for high-grade tumors. Urinary cytology is fairly interpreter-dependent, and detection of cancer can be improved by collection of barbotage samples, multiple samples (at least three consecutive specimens), and urine samples that are not given in the early morning. This test is useful in both the initial diagnosis and surveillance settings.

Many biomarker-based assays have been developed and validated for use in diagnosis or surveillance of urothelial cancer (Mbeutcha et al, 2016). However, despite FDA approval, they are not recommended as replacements for cystoscopic evaluation, and their role remains limited (Chang et al, 2016).

The bladder tumor antigen (BTA) test is an assay for the detection of human complement factor H-related protein in the urine. The BTA-TRAK test is quantitative assay, and the BTA-STAT test is its qualitative, point-of-care counterpart. Both are more sensitive than cytology (especially for low-grade cancers) but less specific. The BTA test is unreliable in patients with active infection and those who have received intravesical therapy. The nuclear matrix protein 22 test (NMP22) is an immunoassay for urinary levels of NMP22, which are elevated in patients with urothelial carcinoma (Grossman et al, 2005). Like BTA testing, other urologic conditions can increase NMP22 levels, leading to false positives (Boman et al, 2018). Compared with cytology, NMP22 is more sensitive for detecting low-grade tumors but is equivalent in the detection of high-grade cancers. The UroVysion fluorescence in situ hybridization (FISH) test detects increased copy numbers of chromosomes 3, 7, 17, and deletions at 9p21. Like other bladder tumor markers, it can improve the sensitivity of urine cytology. Unlike other tests, however, UroVysion FISH can be used in monitoring patients who have undergone intravesical chemotherapy or adjudicating an equivocal cytology result (Mengual et al, 2007). The characteristics of these bladder cancer tests and others are compared in Table 5–1 (Konety, 2018; Mowatt et al, 2010; Konety and Getzenberg, 2018).

B. Prostate Cancer Tests

Prostate cancer tests using voided urine are generally performed on samples obtained after digital rectal exam (DRE).

1. PCA3—PCA3 is a noncoding RNA gene that is highly overexpressed by prostate cancer cells (Bussemakers et al, 1999). The PCA3 test detects PCA3 mRNA levels in the urine and has been FDA approved for use in men with a previous negative prostate biopsy. Depending on the cutoff used, PCA3 can improve risk prediction and potentially avoid unnecessary biopsies while missing a low number of high grade cancers and aid in deciding whether to proceed with repeat biopsy after initial negative biopsy (Haese et al, 2008; Wei et al, 2014).

2. TMPRSS2: ERG—The incidence of the transmembrane protease serine 2: ERG (TMPRSS2: ERG) gene fusion was found to be higher in prostate cancer cells than nonmalignant prostate tissue, and the gene product is detectable in voided urine. The TMPRSS2: ERG assay has been shown to be associated with aggressive prostate cancer, and can increase

Table 5–1. Comparison of different urine tests for bladder transitional cell carcinoma.

Test	Sensitivity (%)	Specificity (%)
Hemoglobin dipstick	71	67
NMP22	68	79
BTA-TRAK	62	74
BTA-STAT	69	74
FDP	68	78
Telomerase	75	86
ImmunoCyt	84	75
UroVysion FISH	76	85
Flow cytometry	59	84
BLCA-4	96	100
Lewis X	80	86
Hyaluronidase	100	89
Hyaluronic acid	92	93
Survivin	100	87
Microsatellite DNA	72	80
Cytology	44	96

BTA, bladder tumor antigen; FDP, fibrin/fibrinogen degradation products; NMP22, nuclear matrix protein 22.

Data from Konety BR, Getzenberg RH: Urine based markers of urological malignancy, J Urol. 2001 Feb;165(2):600–601.

the specificity of detecting aggressive prostate cancer while maintaining a high sensitivity (Sanda et al, 2017). Used alone and in combination with PCA3, it can risk stratify patients on active surveillance and improve the detection of high-risk prostate cancer (Tomlins et al, 2016; Lin et al, 2013).

3. ExoDx Prostate Intelliscore—ExoDx Prostate Intelliscore is an emerging exosome-derived gene expression signature measuring exosomal ERG, PCA3, and ETS transcription factor mRNA in voided urine without prior DRE (McKiernan et al, 2016). Initial evidence suggests it can improve the discrimination between patients with benign/low-grade prostate cancer (Gleason ≤6) and high-grade prostate cancer (Gleason ≥7). This test has yet been widely validated or incorporated into clinical pathways.

4. SelectMDx—SelectMDx is another emerging urinary biomarker for prostate cancer, which measures a three-gene panel expression (DLX1, TDRD1, and HOXC6) (Leyten et al, 2015). This has been shown to provide high accuracy for prediction of high-grade prostate cancer (AUC 0.90) in a limited cohort; however, external validation will be necessary to confirm these results (Neste et al, 2016).

C. Hormonal Studies

A 24-hour urinary free cortisol has been used for diagnosis of Cushing syndrome. However, given problems with poor collection and low sensitivity, it has been superseded in clinical utility by salivary cortisol evaluation (Viardot et al, 2005). Pheochromocytoma and neuroblastoma can be detected by measuring the urinary excretion of vanillylmandelic acid (VMA) and homovanillic acid (HVA) as either 24-hour collections or spot analyses (Cangemi et al, 2013). However, serum and urinary levels of metanephrine, epinephrine, and norepinephrine are more sensitive indicators, particularly in cases of pheochromocytoma, with sensitivity and specificity of 98% (Sawka et al, 2003). Although high levels of aldosterone in urine usually indicate an aldosterone-secreting tumor, drug interference may cause false-positive or false-negative results. Other adrenocortical tumors may be detected by their production of elevated levels of urinary 17-ketosteroids.

D. Studies of Stone Constituents

Patients with recurrent urolithiasis may have an underlying abnormality of excretion of calcium, uric acid, oxalate, magnesium, cysteine, or citrate. Samples of 24-hour urine collections can be tested to determine abnormally high levels of each, along with assessment of adequate hydration (Curhan et al, 2001). The nitroprusside test, a simple *qualitative* screening test for the presence of urinary cystine, may indicate the need for quantifying cystine levels in timed urine collections (Finocchiaro et al, 1998). Whenever a stone is recovered, a formal stone analysis is recommended.

E. Miscellaneous Studies

In patients with suspected fistulas of the urinary tract and bowel (eg, cancer of the colon, diverticulitis, and regional ileitis), discoloration of the urine after ingestion of a poorly absorbed dye such as phenol red will confirm the diagnosis. In an equally satisfactory test for fistulas, the patient is instructed to ingest gelatin capsules filled with granulated charcoal and to submit a urine sample several days later. Examination of the centrifuged urinary sediment will reveal the typical black granules if a fistula is present. In patients with suspected vesicovaginal fistulas, intravesical instillation of methylene blue or indigo carmine dye with resultant blue staining of a vaginal tampon can assist in diagnosis.

EXAMINATION OF URETHRAL DISCHARGE AND VAGINAL EXUDATE

▶ Urethral Discharge

Examination of urethral discharge in males can be particularly helpful in establishing a diagnosis. The following procedure, although exacting, provides proper specimens to identify the origin of bacteriuria or pyuria. Four sterile containers are labeled VB_1, VB_2, EPS, and VB_3 (VB = voided bladder urine; EPS = expressed prostatic secretions). The patient is instructed to retract the foreskin and cleanse the meatus and to collect the urine specimens, capping the containers immediately afterward. The initial 10–15 mL of urine is collected in container VB_1 and the subsequent 15–30 mL in container VB_2. The prostate is then massaged, and secretions are collected in container EPS. The patient voids a final time, collecting the specimen in container VB_3. An aliquot of each specimen is tested for nitrite and leukocyte esterase and then centrifuged, and the sediment is prepared for microscopic examination as described previously. A separate aliquot of each VB specimen and the EPS specimen are saved for subsequent culture if necessary. The presence of leukocytes or bacteria (or both) only in VB_1 indicates anterior urethritis; if present in all three VB specimens, they may indicate cystitis or upper urinary tract infection; if present in EPS or VB_3 only, they indicate a prostatic source of infection. Alternatively, a simpler two-sample test (pre- and postprostatic massage) has been shown to yield similar diagnostic information with more reliable collection and lower cost (Nickel et al, 2018). Quantitative cultures can be similarly interpreted.

If the patient presents with the thick yellowish discharge typical of *Neisseria gonorrhoeae* infection, the discharge should be stained with Gram's stain and examined for Gram-negative intracellular diplococci. It is important to remember that commensal bacteria in smegma may produce false-positive results.

If the patient presents with clear or whitish urethral discharge, a smear of the discharge obtained by milking the urethra or from VB_1 should be stained with methylene blue or Gram's stain and examined microscopically. The presence of trichomonads, yeast cells, or bacteria in properly collected specimens indicates disease requiring treatment.

In cases of acute epididymitis, urinalysis and urine culture are often helpful in establishing the cause. Epididymitis is most commonly caused by *Chlamydia* species in young men and by *Escherichia coli* in men older than 35 years. Culturing chlamydiae is time-consuming and expensive. Although a rapid immunofluorescence method of identifying *Chlamydia* is available, it is usually best to proceed with therapy based on the age of the patient and guided by clinical results. Of note, any patients being screened for sexually transmitted infections should also be tested for HIV (Workowski and Bolan, 2015).

Vaginal Exudate

The underlying cause of vaginitis is often a viral, yeast, or protozoal infection or the presence of a foreign body (eg, retained tampon), and a simple physical examination may be all that is required for diagnosis. Vaginal secretions obtained by use of a swab can be examined either stained or unstained. A drop of saline is added to a drop of specimen on a glass slide, mixed thoroughly, and covered with a coverslip. Examination under a low- or high-power lens may reveal yeast cells or trichomonads, thus suggesting appropriate therapy. Since bacteria are always present in the vagina, they seldom are significant findings in a wet smear. A potassium hydroxide (KOH) wet mount can be helpful for identifying hyphae and yeast, and the presence of a fishy, amine odor after application of KOH can indicate bacterial vaginosis.

RENAL FUNCTION TESTS

Urine Specific Gravity

With diminished renal function, the ability of the kidneys to concentrate urine lessens progressively until the specific gravity of urine reaches 1.006–1.010. However, the ability to dilute urine tends to be maintained until renal damage is extreme. Even in uremia, although the concentrating power of the kidneys is limited to a specific gravity of 1.010, dilution power in the specific gravity range of 1.002–1.004 may still be found. Determination of urine osmolality is undoubtedly a more meaningful measurement of renal function, but determination of specific gravity lends itself to office diagnosis.

Serum Creatinine

Creatinine, the end product of the metabolism of creatine in skeletal muscle, is normally excreted by the kidneys. Because individual daily creatinine production is constant, the serum level is a direct reflection of renal function. Serum creatinine levels remain within the normal range (0.8–1.2 mg/dL in adults; 0.4–0.8 mg/dL in young children) until approximately 50% of renal function has been lost. Unlike most other excretory products, the serum creatinine level generally is not influenced by dietary intake.

Glomerular Filtration Rate

Although there are limitations to the use of serum creatinine for estimation of glomerular filtration rate (eGFR), such as variations in production, secretion, and measurement of creatinine, it remains a useful measure of renal function. Various equations are available for estimating GFR, such as the Cockcroft–Gault, MDRD, and CKD-EPI. However research has shown the CKD-EPI provides more accurate estimates when GFR is high and also more accurately predicts risk of end-stage renal disease, cardiovascular mortality, and all-cause mortality (Matsushita et al, 2012).

Endogenous Creatinine Clearance

Because creatinine production is stable and creatinine is filtered through the glomerulus (although a small amount is secreted), its renal clearance is essentially equal to the glomerular filtration rate. The endogenous creatinine clearance test has thus become the most accurate and reliable measure of renal function available without resorting to infusion of exogenous substances such as radionuclides. Determination of creatinine clearance requires only the collection of a timed (usually 24-hour) urine specimen and a serum specimen. The resulting clearance is expressed in milliliters per minute, with 90–110 mL/min considered normal.

Because muscle mass differs among individuals, further standardization has been achieved, and a corrected clearance level of 70–140 mL/min is considered normal. Although creatinine is highly reliable as an estimate of renal function, values may be falsely low, particularly if only part of the urine is collected over the time period or if a serum specimen is not collected concurrently.

Blood Urea Nitrogen

Urea is the primary metabolite of protein catabolism and is excreted entirely by the kidneys. The blood urea nitrogen (BUN) level is therefore related to the glomerular filtration rate. However, unlike creatinine, BUN is influenced by dietary protein intake, hydration status, and gastrointestinal bleeding. Approximately two-thirds of renal function must be lost before a significant rise in BUN level becomes evident. For these reasons, an elevated BUN level is less specific for renal insufficiency than an elevated serum creatinine level. However, the BUN: creatinine (BUN: Cr) ratio can provide specific diagnostic information. It is normally 10:1; in dehydrated patients and those with bilateral urinary obstruction or urinary extravasation, the ratio may range from 20:1 to 40:1; patients with advanced hepatic insufficiency and overhydrated patients may exhibit a lower than normal BUN level and BUN:Cr ratio. In patients with renal insufficiency, extremely high BUN levels may develop that can be partially controlled by a decrease in dietary protein.

EXAMINATION OF BLOOD, SERUM, AND PLASMA

Complete Blood Count

Normochromic normocytic anemia is often seen with chronic renal insufficiency. Chronic blood loss from microscopic hematuria is seldom severe enough to cause anemia, although gross hematuria certainly can be. A specific increase in the number of erythrocytes, as manifested by elevated hemoglobin and hematocrit levels (erythrocytosis, not polycythemia), may be indicative of a paraneoplastic syndrome associated with renal cell cancer. The leukocyte count is usually nonspecific, although marked elevations may indicate an underlying leukemia that may be the cause of urologic symptoms.

Blood Clotting Studies

Clotting studies are seldom necessary unless an insidious disorder such as von Willebrand disease, hepatic disease, or sensitivity to ingested salicylates is suspected in a patient with unexplained hematuria. Determinations of prothrombin time and partial thromboplastin time usually suffice. A platelet count is important in patients receiving chemotherapy and those who have received extensive radiation therapy.

Electrolyte Studies

Serum sodium and potassium determinations may be indicated in patients taking diuretics and select postoperative patients, such as those who do not have any oral intake or have undergone transurethral resections of prostate with sterile water or glycine irrigation. Serum calcium (along with parathyroid hormone) determinations are useful in patients with calcium urolithiasis. Elevated calcium levels are occasionally indicative of a paraneoplastic syndrome in patients with renal cell cancer. Serum albumin levels should be measured simultaneously with calcium levels to adequately assess the significance of the latter.

Prostate Cancer Markers

Prostate-specific antigen (PSA) is an important, if controversial, prostate cancer marker. PSA is prostate-specific but not cancer-specific. Levels vary with prostate volume, number of benign prostate glands, inflammation, and amount of cancer within the gland. PSA has become useful as a screening tool and is most useful as a marker of effective treatment (it falls to zero following removal of organ-confined cancer) and early recurrence. The percentage of free PSA (ratio of unbound to total PSA) in the serum is useful for increasing the specificity of PSA for diagnosing prostate cancer. The use of PSA for prostate cancer screening is a topic of considerable debate and will be explored more in the chapter dedicated to prostate cancer (Chapter 21).

The Prostate Health Index (PHI), which combines the total PSA, free PSA, and [−2] proPSA, can provide a risk predictor for the presence of high-grade prostate cancer (Gleason ≥4+3) (Catalona 2018). PSA is 1 of 15 serine proteases from the kallikrien family (human kallikrien 3). The 4KScore is composed of measurement of four kallikrien-based biomarkers (total PSA, free PSA, intact PSA, and human kallikrien 2) levels (Vickers et al, 2008). Its use has been shown to lead to an 8–13% improvement in prediction accuracy for high-grade disease while avoiding nearly 50% of biopsies and missing 1–4% of high-grade cancers (Parekh et al, 2018). Both the PHI and 4KScore can be useful in identifying patients who should undergo prostate biopsy, both initial biopsy and repeat after a negative biopsy.

Testis Cancer Markers

Determinations of serum levels of the β subunit of human chorionic gonadotrophin (hCG), α-fetoprotein (AFP), and lactate dehydrogenase (LDH) are critical in staging and surveillance for testis cancer. For staging, markers must be drawn three to five half-lives after radical orchiectomy, with each half-life between 24 and 36 hours for hCG and 5–7 days for AFP. One of these tumor markers is usually elevated in up to 85% of patients with nonseminomatous testicular tumors.

Hormonal Studies

Serum parathyroid hormone studies are useful in determining the presence of a parathyroid adenoma in patients with urolithiasis and elevated serum calcium levels. Measurement of parathyroid hormone is not reliable, however, as a sole screening test for parathyroid adenoma and should not be used routinely in all patients with urolithiasis. Serum renin levels may be elevated in patients with renal hypertension, although many conditions can cause false-positive results. Studies of adrenal steroid hormones (eg, aldosterone, cortisol, epinephrine, and norepinephrine) are useful in determining adrenal function or the presence of adrenal tumors. Serum testosterone studies can help to establish the cause of impotence or infertility. (See Tables 5–2 and 5–3.)

Table 5–2. Laboratory values that do not change with age.

Hepatic function tests
Serum bilirubin
AST
ALT
GGTP
Coagulation tests
Biochemical tests
Serum electrolytes
Total protein
Calcium
Phosphorus
Serum folate
Arterial blood tests
pH
$PaCO_2$
Renal function tests
Serum creatinine
Thyroid function tests
T_4
Complete blood count
Hematocrit
Hemoglobin
Erythrocyte indices
Platelet count

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP, gamma-glutamyltransferase.

Table 5–3. Laboratory values that do change with age.

Value	Degree of change
Alkaline phosphatase	Increases by 20% between third and eighth decades
Biochemical tests	
Serum albumin	Slight decline
Uric acid	Slight increase
Total cholesterol	Increases by 30–40 mg/dL by age 55 in women and age 60 in men
HDL cholesterol	Increases by 30% in men; decreases by 50% in women
Triglycerides	Increases by 30% in men and 50% in women
Serum B_{12}	Slight decrease
Serum magnesium	Decreases by 15% between third and eighth decades
PaO_2	Decreases by 25% between third and eighth decades
Creatinine clearance	Decreases by 10 mL/min/1.73 sq m/decade
Thyroid function tests	
T_3	Possible slight decrease
TSH	Possible slight increase
Glucose tolerance tests	
Fasting blood sugar	Minimal increase (within normal range)
1-Hour postprandial blood sugar	Increases by 10 mg/dL/decade after age 30
2-Hour postprandial blood sugar	Increases up to 100 plus age after age 40
Leukocyte count	Decreases

HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone.

Note: Other factors that may make laboratory interpretation more difficult include atypical disease presentation, multiple concurrent diseases, and prescription and nonprescription drug use.

BIBLIOGRAPHY

Introduction

Litwin MS, Saigal CS: Urologic Diseases in America. National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

Examination of Urine

Anonymous: American Society of Anesthesiologists Task Force on Preanesthesia Evaluation: Practice advisory for preanesthesia evaluation. Anesthesiology 2012;116:522–538. (Available online at: http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/ALN.0b013e31823c1067.)

Boman H, Hedelin H, Sten A, et al: Four bladder tumor markers have a disappointingly low sensitivity for small size and low grade recurrence. J Urol 2002;167:80–83. (Available online at:

http://www.jurology.com/article/S0022-5347([05)]65387-6/pdf; accessed 2/7/ 2018.)

Bussemakers MJ, Can Bokhoven A, Verhaegh GW, et al: DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Res 1999;59:5975–5979. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/7538903; accessed 2/7/2018.)

Cangemi G, Barco S, Reggiardo G, et al: Interchangeability between 24-hour collection and single spot urines for vanillylmandelic and homovanillic acid levels in the diagnosis of neuroblastoma. Pediatr Blood Cancer 2013;60:E170–E172. (Available online at: http://doi.wiley.com/10.1002/pbc.24671; accessed 2/8/2018.)

Chang SS, Boorjian SA, Chou R, et al: Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. J Urol 2016;196:1021–1029. (Available online at: http://www.jurology.com/article/S0022-5347([16)]30629-2/pdf; accessed 2/2018.)

Curhan GC, Willett WC, Speizer FE, et al: Twenty-four–hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 2001;59:2290–2298. (Available online at: https://ac.els-cdn.com/S0085253815477257/1-s2.0-S0085253815477257-main.pdf?_tid=9f84a8a0-0d0a-11e8-8b87-00000aacb361&acdnat=1518120171_39eac28b9e928f8a25ac91c7a46ea174; accessed 2/8/ 2018.)

Davis R, Jones JS, Barocas D, et al: American Urological Association (AUA) Guideline ADULTS: AUA GUIDELINE American Urological Association Asymptomatic Microhematuria. J Urol 2012;188:1–30. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/23098784.)

Finocchiaro R, D'Eufemia P, Celli M, et al: Usefulness of cyanide-nitroprusside test in detecting incomplete recessive heterozygotes for cystinuria: A standardized dilution procedure. Urol Res 1998;26:401–405. (Available online at: http://link.springer.com/10.1007/s002400050076; accessed 2/8/2018.)

Gallagher EJ, Schwartz E, Weinstein RS: Performance characteristics of urine dipsticks stored in open containers. Am J Emerg Med 1990;8:121–123. (Available online at: http://www.ajemjournal.com/article/0735-6757(90)90197-8/pdf; accessed 2/7/ 2018.)

Grossman HB, Messing E, Soloway M, et al: Detection of bladder cancer using a point-of-care proteomic assay. JAMA 2005;293:810. (Available online at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.293.7.810; accessed 2/7/2018.)

Haese A, de la Taille A, van Poppel H, et al: Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. Eur Urol 2008;54:1081–1088. (Available online at: http://www.europeanurology.com/article/S0302-2838(08)00778-1/pdf; accessed 2/7/ 2018.)

Hagan JF, Shaw JS, Duncan PM: Guidelines for health supervision of infants, children, and adolescents. American Academy of Pediatrics Guidelines 2017. (Available online at: https://brightfutures.aap.org/BrightFutures Documents/BF4_POCKETGUIDE.pdf; accessed 2/1/2018.)

Hessdoerfer E, Jundt K, Peschers U: Is a dipstick test sufficient to exclude urinary tract infection in women with overactive bladder? Int Urogynecol J 2011;22:229–232. (Available online at: http://link.springer.com/10.1007/s00192-010-1263-5; accessed 2/1/2018.)

Izzedine H, Lescure FX, Bonnet F: HIV medication-based urolithiasis. Clin Kidney J 2014;7:121–126. (Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4377784/pdf/sfu008.pdf; accessed 2/7/2018.)

Khadra MH, Pickard RS, Charlton M, et al: A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol 2000;163:524–527. (Available online at: http://www.jurology.com/article/S0022-5347[(05)]67916-5/pdf; accessed 2/7/2018.)

Konety BR, Getzenberg RH: Urine based markers of urological malignancy. J Urol 2001;165: 600–611. (Available online at: http://www.jurology.com/article/S0022-5347(05)66778-X/pdf; accessed 2/7/2018.)

Konety BR: Molecular markers in bladder cancer: A critical appraisal. Urol Oncol 2006;24:326–337. (Available online at: http://www.urologiconcology.org/article/S1078-1439[05]00287-5/pdf; accessed 2/7/2018.)

Kunin CM, White LV, Hua TH: A reassessment of the importance of low-count bacteriuria in young women with acute urinary symptoms. Ann Intern Med 1993;119: 454. (Available online at: http://annals.org/article.aspx?doi=10.7326/0003-4819-119-6-199309150-00002; accessed 2/7/2018.)

Leyten GHJM, Hessels D, Smit FP, et al: Identification of a candidate gene panel for the early diagnosis of prostate cancer. Clin Cancer Res 2015;21:3061–3070. (Available online at: http://clincancerres.aacrjournals.org/content/clincanres/21/13/3061.full.pdf; accessed 2/8/ 2018.)

Lifshitz E, Kramer L: Outpatient urine culture. Arch Intern Med 2000;160:2537. (Available online at: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.160.16.2537; accessed 2/7/2018.)

Lin DW, Newcomb LF, Brown EC, et al: Urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: Results from a baseline analysis in the canary prostate active surveillance study. Clin Cancer Res 2013;19:2442–2450.

Little P, Turner S, Rumsby K, et al: Dipsticks and diagnostic algorithms in urinary tract infection: Development and validation, randomised trial, economic analysis, observational cohort and qualitative study. Health Technol Assess 2009;13.

Little P, Turner S, Rumsby K, et al: Validating the prediction of lower urinary tract infection in primary care: Sensitivity and specificity of urinary dipsticks and clinical scores in women. Br J Gen Pract 2010;60:495–500.

Mbeutcha A, Lucca I, Mathieu R, et al: Current status of urinary biomarkers for detection and surveillance of bladder cancer. Urol Clin North Am 2016;43:47–62.

McKiernan J, Donovan MJ, O'Neill V, et al: A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. JAMA Oncol 2016;2:882–889.

Mengual L, Marín-Aguilera M, Ribal MJ, et al: Clinical utility of fluorescent in situ hybridization for the surveillance of bladder cancer patients treated with Bacillus Calmette-Guérin therapy. Eur Urol 2007;52:752–759. (Available online at: http://www.europeanurology.com/article/S0302-2838[07]00354-5/pdf; accessed 2/7/2018.)

Mowatt G, Zhu S, Kilonzo M, et al: Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. Health Technol Assess 2010;14:1–331. (Available online at: http://aura.abdn.ac.uk/bitstream/handle/2164/731/Mowatt2010.pdf?sequence=1; accessed 2/7/2018.)

Neste L Van, Hendriks RJ, Dijkstra S, et al: Prostate cancer detection of high-grade prostate cancer using a urinary molecular biomarker—based risk score. Eur Urol 2016;70:740–748. (Available online at: http://dx.doi.org/10.1016/j.eururo.2016.04.012; accessed 2/8/2018.)

Sanda MG, Feng Z, Howard DH, et al: Association between combined TMPRSS2:ERG and PCA3 RNA urinary testing and detection of aggressive prostate cancer. JAMA Oncol 2017;3:1085–1093.

Sawka AM, Jaeschke R, Singh RJ, et al: A comparison of biochemical tests for pheochromocytoma: Measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003;88:553–558. (Available online at: https://watermark.silverchair.com/jcem0553.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAdAwggHMBgkqhkiG9w0BBwagggG9MIIBuQIBADCCAbIGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQM8rZhm-;v2Sheq2ZjtAgEQgIIBg50hPm2Z5fpI2C2Dh4avPpyNans_4WTyLusM_k1smuN1ed; accessed 2/8/2018.)

Simerville JA, Maxted WC, Pahira JJ: Urinalysis: A comprehensive review. Am Fam Physician 2005.

Tomlins SA, Day JR, Lonigro RJ, et al: Urine TMPRSS2:ERG plus PCA3 for individualized prostate cancer risk assessment. Eur Urol 2016;70:45–53. (Available online at: http://dx.doi.org/10.1016/j.eururo.2015.04.039; accessed 2/7/2018.)

Viardot A, Huber P, Puder JJ, et al: Reproducibility of nighttime salivary cortisol and its use in the diagnosis of hypercortisolism compared with urinary free cortisol and overnight dexamethasone suppression test. J Clin Endocrinol Metab 2005;90:5730–5736. (Available online at: https://watermark.silverchair.com/jcem5730.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAdEwggHNBgkqhkiG9w0BBwagggG-MIIBugIBADCCAbMGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQM_3eDGcSpDTsxUNp7AgEQgIIBhODrY9-syTDDaG6iPcCisiJgqJK6aHpNXkMNsjWkeUQHjN; accessed 2/8/2018.)

Wei JT, Feng Z, Partin AW, et al: Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol 2014;32:4066–4072. (Available online at: http://ascopubs.org/doi/10.1200/JCO.2013.52.8505; accessed 2/7/2018.)

Witte EC, Lambers Heerspink HJ, de Zeeuw D, et al: First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am Soc Nephrol 2009;20:436–443. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/19092125; accessed 2/1/ 2018.)

Discharge and Vaginal Exudate

Nickel JC, Shoskes D, Wang Y, et al: How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? J Urol 2006;176:119–124. (Available online at: http://www.jurology.com/article/S0022-5347[06]00498-8/pdf; accessed 2/8/18.)

Workowski KA, Bolan GA: Sexually transmitted diseases treatment guidelines, 2015. MMWR (Morbidity and Mortality Weekly Report) 2015;64:1–137.

Renal Function Tests

Matsushita K, Mahmoodi BK, Woodward M, et al: Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA 2012;307:1941–1951. (Available online at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.3954; accessed 2/8/18.)

Examination of Blood, Serum, and Plasma

Catalona WJ, Partin AW, Sanda MG, et al: A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol 2011;185:1650–1655. (Available online at: http://www.jurology.com/article/S0022-5347[10]05374-7/pdf; accessed 2/8/18.)

Parekh DJ, Punnen S, Sjoberg DD, et al: A multi-institutional prospective trial in the USA confirms that the 4K score accurately identifies men with high-grade prostate cancer. Eur Urol 2015;68:464–470. (Available online at: http://dx.doi.org/10.1016/j.eururo.2014.10.021; accessed 2/8/18.)

Vickers AJ, Cronin AM, Aus G, et al: A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: Data from the European Randomized Study of Prostate Cancer Screening in Göteborg, Sweden. BMC Med 2008;6. (Available online at: http://www.biomedcentral.com/1741-7015/6/19; accessed 2/8/18.)

This page intentionally left blank

Radiology of the Urinary Tract

6

Daniela Franz, MD; Scott Gerst, MD; &
Hedvig Hricak, MD, PhD

The pace of innovation in diagnostic radiology has increased exponentially, in tandem with computer advances and the rapid evolution of microprocessing power. Imaging of the urinary tract, as a result, has become more flexible and precise, with new procedures offering a great selection of options and the implementation of new imaging algorithms. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) provide higher soft-tissue contrast resolution than conventional radiography, as well as multiplanar imaging capability, resulting in significant advances in almost all areas of uroradiology. In academic centers, metabolic and molecular imaging techniques have become the focus of new research and have begun to enter the realm of daily clinical practice. While imaging advances have produced new algorithms for approaching diagnostic evaluation, appropriate use of imaging in each individual case also depends greatly on the equipment and professional talent available. One imaging modality or protocol may offer specific advantages over another, depending on the clinical question, and the importance of a collaborative approach from the medical team cannot be overemphasized.

In summary, ever-changing uroradiology remains indispensable in the diagnosis and treatment of patients with urologic disorders. This chapter discusses the imaging techniques used in uroradiology and summarizes the advantages and disadvantages of the various techniques and concludes with a brief discussion comparing imaging methods.

RADIOGRAPHY

X-rays are electromagnetic waves with photon energies that typically fall between those of gamma (γ) rays and ultraviolet radiation. Radiography is possible because tissues differ in their ability to absorb x-rays. A radiopaque contrast medium is frequently employed to enhance soft-tissue contrast.

Although newer imaging techniques have largely replaced conventional radiography for diagnosis of many urologic problems, general radiography remains useful for some urologic disorders; therefore, the urologist should be familiar with x-ray equipment and uroradiologic techniques. The basic types of uroradiologic studies are plain (conventional) abdominal films (also known as **kidney–ureter–bladder [KUB] films**), intravenous urograms (IVUs), cystourethrograms, urethrograms, and angiograms. These studies are described separately in sections that follow.

Basic Equipment and Techniques

1. Radiography fluoroscopy—Many conventional x-ray units contain both radiographic and fluoroscopic capabilities. These require a high-voltage power supply, an x-ray tube, a collimating device, and an x-ray detector or film. Fluoroscopic units also use an electronic image intensifier and an image display system. Today, most radiology departments have become completely “filmless” as digital recording, displaying, and archiving of images are replacing film-based techniques.

2. Image intensification—Image intensifiers, coupled to videocameras, electronically augment the ordinary dim fluoroscopic image.

3. Image recording—Conventional recording of an x-ray image uses film and intensifying screens. The image intensifier and camera can be used to capture dynamic and static images. Real-time images are now typically recorded using conventional or digital video. Conventional spot or cine images may be acquired on x-ray film or digitally recorded.

4. Contrast media—Radiographic contrast media used in uroradiography are water-soluble iodinated compounds that are radiopaque. Similar compounds are used for basic radiographic techniques and CT, although iodine concentrations will differ depending on preference and route of administration. In general, intravenous administration for CT or IVU is performed with iodine 200 mg/lb body weight in adults, and direct instillation to the collecting system or bladders uses similar media diluted to 15–45% concentration. The extracellular distribution of these agents results in improved contrast resolution and conspicuity of various structures.

Significant advances in water-soluble contrast media occurred with the introduction of low-osmolality, nonionic organic iodine-containing compounds. These nonionic agents significantly improve patient tolerance and decrease the incidence of adverse reactions, and at many institutions the use of nonionic agents is standard. Whether they reduce the mortality associated with the use of contrast media has not been proven. The major obstacle to their use is higher cost.

5. Adverse reactions—All procedures using intravascular contrast media carry a small but definite risk of adverse reactions. The overall incidence of adverse reactions is about 5%, while a lower incidence of 0.34% has been reported for nonionic contrast media (Li et al, 2015). Reactions in nonintravenous use (ie, cystograms) are extremely rare but have been reported.

Most reactions are minor (eg, nausea, vomiting, hives, rash, or flushing) and usually require only patient reassurance. Cardiopulmonary and anaphylactoid reactions can occur with little warning and can be life-threatening or fatal. In a large meta-analysis, the incidence of death due to intravascular injection of contrast media was 0.9 death per 100,000 injections. There are no reliable methods for pretesting patients for possible adverse reactions. The risks and benefits of contrast use should be carefully evaluated for each patient before the procedure is initiated. Treatment of adverse reactions involves the use of antihistamines, epinephrine, vascular volume expanders, bronchodilators, and other cardiopulmonary drugs as well as ancillary procedures indicated by the nature and severity of the reaction. In some cases, a radiographic examination using intravascular contrast media is critical even if the patient has had a prior moderate or severe reaction. Such patients are given nonionic contrast agents and pretreated with corticosteroids, sometimes in combination with antihistamines, to prevent recurrence. This preventive treatment is not always successful, so any decision to administer contrast under these circumstances should be carefully weighed against the risks.

Nephrotoxicity caused by intravascular contrast agents is another concern. The pathogenesis of contrast nephropathy (CN) likely involves medullary ischemia due to contrast-induced vasoconstriction and direct tubular injury. Patients at higher risk are those with preexisting renal insufficiency, diabetes, or dehydration, or patients who receive higher volumes of contrast material. Alternative procedures can be selected in high-risk patients. If contrast use is deemed necessary in a high-risk individual, CN can be minimized through attention to proper hydration, discontinuation of drugs that may exacerbate toxic effects, adequate hydration in the 24 hours prior to scanning, reduction of contrast volume, and possibly administration of oral *N*-acetylcysteine.

Advantages and Disadvantages

Radiography produces anatomic images of almost any body part. Costs are moderate compared with cross-sectional imaging systems. Space requirements are modest, and portable equipment is available for use in hospital wards, operating rooms, and intensive care units. Because there are a great many specialists trained in radiography, its use is not confined to large medical centers. The major disadvantage of radiographic imaging is the use of ionizing radiation and relatively poor soft-tissue contrast. The evaluation of the urinary tract almost always requires opacification by iodine contrast media.

1. Plain film of the abdomen (Figures 6–1 to 6–3)—A plain film of the abdomen, frequently called a **KUB film** (as noted above), is the simplest uroradiologic examination. It is generally the preliminary radiograph in extended radiologic examinations, such as intravenous urography, and is usually taken with the patient in supine position. It may demonstrate osseous abnormalities, abnormal calcifications, or large soft-tissue masses.

Kidney outlines usually can be seen on the plain film, so that their size, number, shape, and position can be assessed. The size of the normal adult kidney varies widely. The long diameter (the length) of the kidney is the most widely used and most convenient radiographic measurement. The average adult kidney is about 12–14 cm long. In children older than 2 years of age, the length of a normal kidney is approximately equal to the distance from the top of the first to the bottom of the fourth lumbar vertebral body. Patterns of calcification in the urinary tract (Figures 6–1 and 6–2) may help identify specific diseases.

2. Urography (Figures 6–4 to 6–8)—The collecting structures of the kidneys, ureters, and bladder can be demonstrated radiologically with contrast media by the methods described in the following sections.

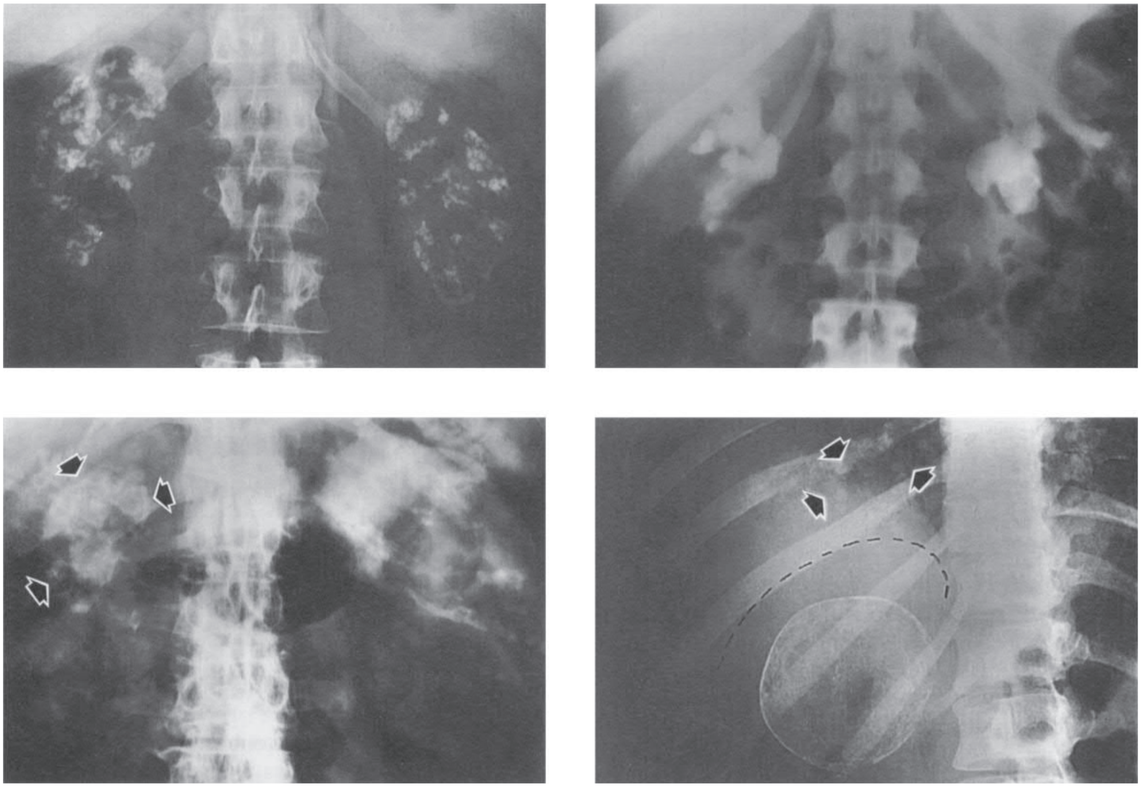
Intravenous Urography

The IVU, also known as **excretory urography (EU)** (Figure 6–4) or **intravenous pyelography (IVP)**, can demonstrate a wide variety of urinary tract lesions (Figures 6–4 and 6–5), is simple to perform, and is well tolerated by most patients.

Computed tomography, sonography, and MRI have replaced urography in most cases. Nevertheless, urography is occasionally used and is useful for demonstrating small lesions in the urinary tract (eg, papillary necrosis, medullary sponge kidney, uroepithelial tumors, pyeloureteritis cystica).

A. Patient Preparation

At one time dehydration was advocated as optimal preparation for IVP. This is no longer required. Furthermore,



▲ **Figure 6–1.** Plain films of the abdomen with abnormal radiopacities. ***Upper left:*** Bilateral nephrocalcinosis. Young adult male with renal tubular acidosis. ***Upper right:*** Bilateral staghorn calculi. A 37-year-old woman with chronic pyelonephritis and history of previous right staghorn pyelolithotomy. ***Lower left:*** Renal tuberculosis. Shrunken, autonephrectomized, and calcified right tuberculous kidney (*arrows*). A 74-year-old man with history of renal and thoracolumbar spinal tuberculosis. ***Lower right:*** Papillary adenocarcinoma of right kidney. Remarkable tumor surface calcifications. Multiple pulmonary metastases (*arrows*) from the renal cancer. A 22-year-old woman with painless soft-tissue mass in the neck.

dehydration is to be avoided in infants; debilitated and elderly patients; and patients with diabetes mellitus, renal failure, multiple myeloma, or hyperuricemia.

It is controversial whether preliminary bowel cleansing is beneficial. The choice may be made according to individual preference.

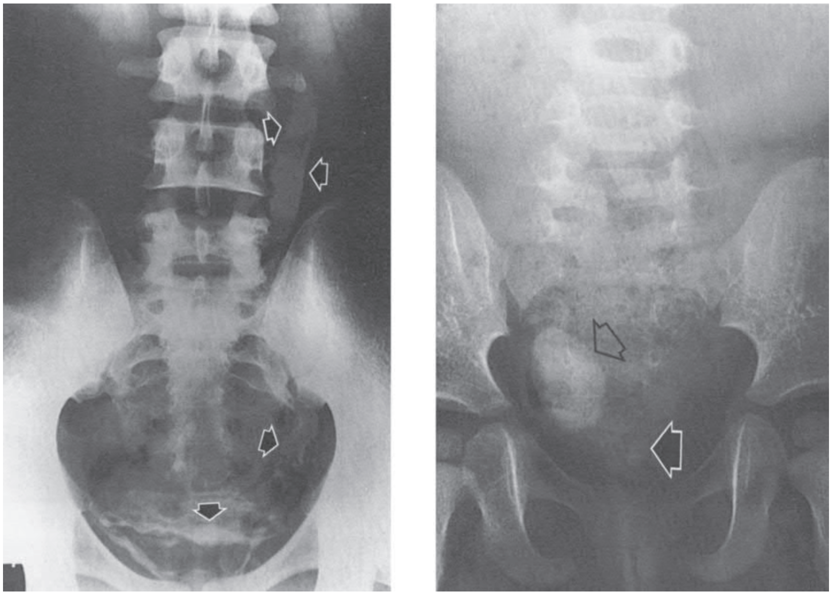
B. Standard Technique

Following a preliminary plain film of the abdomen, additional radiographs are taken at timed intervals after the intravenous injection of iodine-containing contrast medium. Normal kidneys promptly excrete contrast agents, almost entirely by glomerular filtration.

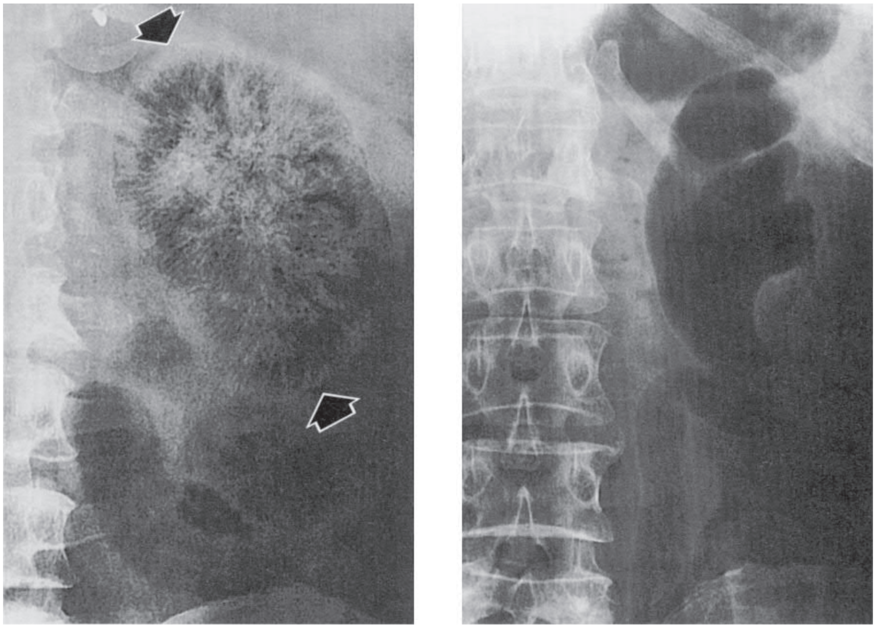
The volume and speed of injection of the contrast medium, as well as the number and type of films taken, vary by preference, patient tolerance, and the specific clinical scenario.

C. Technique Modifications

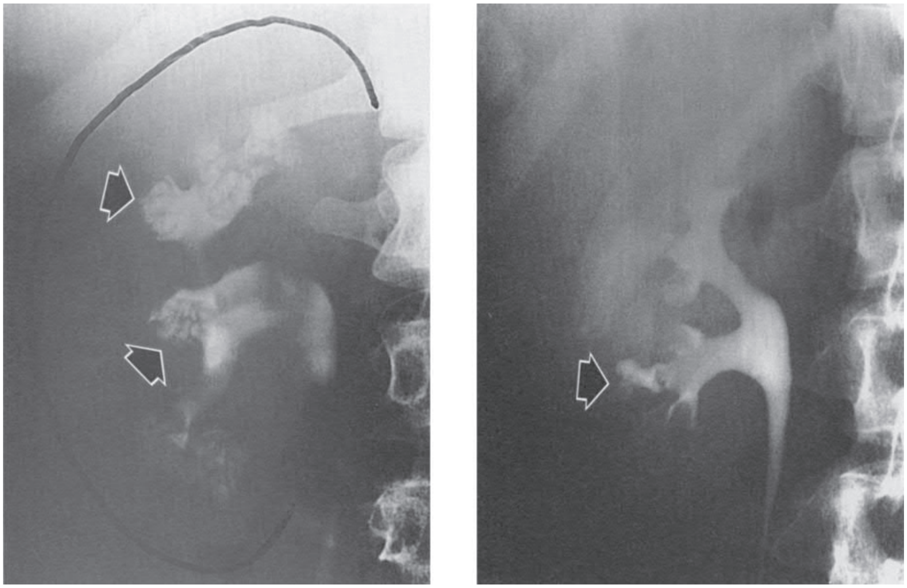
The standard technique can be modified in several ways; however, the modifications have largely been replaced by cross-sectional imaging modalities. Before the rise of cross-sectional imaging, radiographic tomography, or x-ray imaging of a selected plane in the body, permitted recognition of kidney structures that otherwise were obscured on standard radiograms by extrarenal shadows, such as those due to bone or feces (Figure 6–4). “Immediate” films, which were taken immediately after the rapid (bolus) injection of contrast, typically showed a dense nephrogram and permitted better visualization of renal outlines. Some of the modified techniques are still being used today. Image-intensified fluoroscopy permits study of urinary tract dynamics. Abdominal (ureteral) compression devices temporarily obstruct the upper urinary tract during EU and improve the filling of renal collecting structures. “Delayed” films, taken hours later or on the



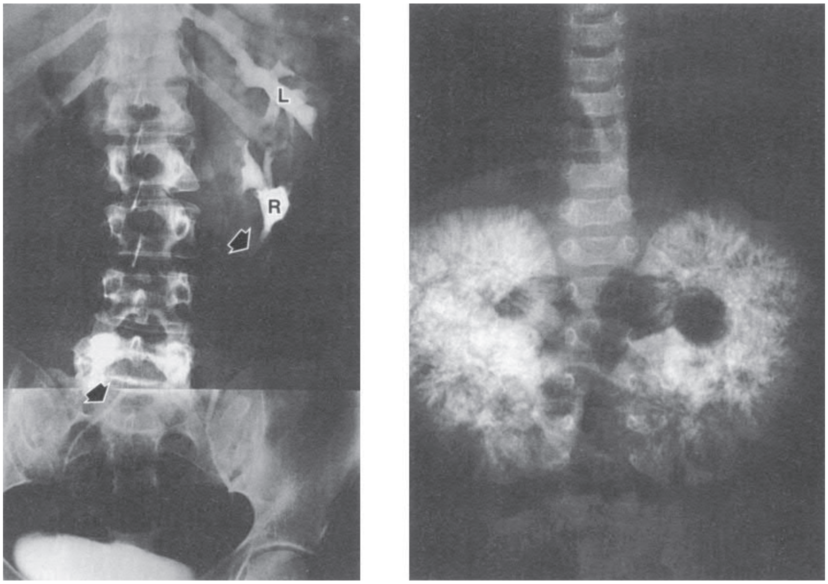
▲ **Figure 6–2.** Plain films of the abdomen with abnormal radiopacities. ***Left:*** Schistosomiasis calcification (*arrows*) in bladder and left ureter. A 19-year-old boy native of Aden with weight loss and hematuria. ***Right:*** Large vaginolith (*open arrow*) and small, barely visible bladder calculus (*solid arrow*). A 4-year-old girl with common urogenital sinus.



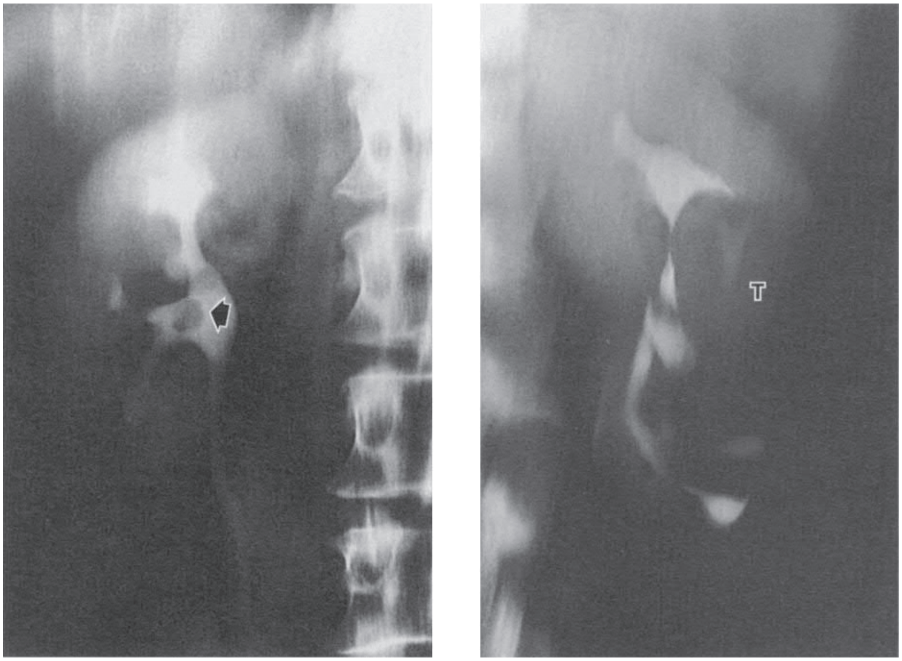
▲ **Figure 6–3.** Plain films of the abdomen with abnormal radiolucencies. ***Left:*** Emphysematous pyelonephritis. Interstitial striated pattern of radiolucent gas throughout the entire left kidney. Similar changes were present in the right kidney. A 58-year-old diabetic man with pyuria and septic shock. ***Right:*** Gas pyelogram. No interstitial gas, but gas fills dilated left kidney calices, pelvis, and ureter. A 50-year-old diabetic woman with sepsis and left upper urinary tract infection due to gas-forming microorganisms.



▲ **Figure 6–4.** Abnormal excretory urograms. ***Left:*** Medullary sponge kidney. Pronounced medullary tubular ectasia (*arrows*) of entire right kidney. Similar findings were present in upper pole pyramids of left kidney, and small medullary calculi were present in some areas of tubular ectasia in both kidneys. A 34-year-old woman with repeated bouts of chills, fever, and left flank pain. ***Right:*** Renal tuberculosis. Irregular cavitation of lower pole pyramid (*arrow*). A 22-year-old woman with positive urine culture for tuberculosis.



▲ **Figure 6–5.** Abnormal excretory urograms. ***Left:*** Crossed fused ectopia. Composite of two films from an excretory urogram shows ectopic right kidney (R) fused to left kidney (L). Right ureter (*arrows*) crosses midline and enters normally into right side of bladder. Healthy 31-year-old woman potential kidney donor. ***Right:*** Infantile polycystic kidney disease. Very large kidneys with radiopaque spoke pattern radiating out to cortex. At 26 hours after administration of intravenous contrast medium. A 4-month-old girl with bilateral abdominal masses.



▲ **Figure 6–6.** Radiographic tomography. Tomography is used to image a plane in the body. The technique was widely used in uroradiology, often permitting demonstration of lesions otherwise hidden by overlying soft tissues or obscuring bowel shadows. However, computed tomography (CT) is rapidly replacing conventional excretory urograms, and thus the use of tomography is declining as well. ***Left:*** Transitional cell carcinoma. The tumor in the pelvis (*arrow*) is clearly shown free of obscuring gas shadows present on the nontomographic films. A 56-year-old man with history of renal calculi. ***Right:*** Renal cell carcinoma (T). Displacement of midkidney collecting structures and a nephrogram defect are seen free of obscuring splenic flexure fecal shadows that were present on the nontomographic films. A 44-year-old woman with fever, weight loss, anemia, and history of contralateral nephrectomy for carcinoma 15 years earlier.

following day, can contribute useful information. "Upright" films, taken with the patient standing or partially erect, reveal the degree of mobility and drainage of the kidneys and, if taken immediately after the patient has voided ("postvoiding" film), show any residual urine in the bladder.

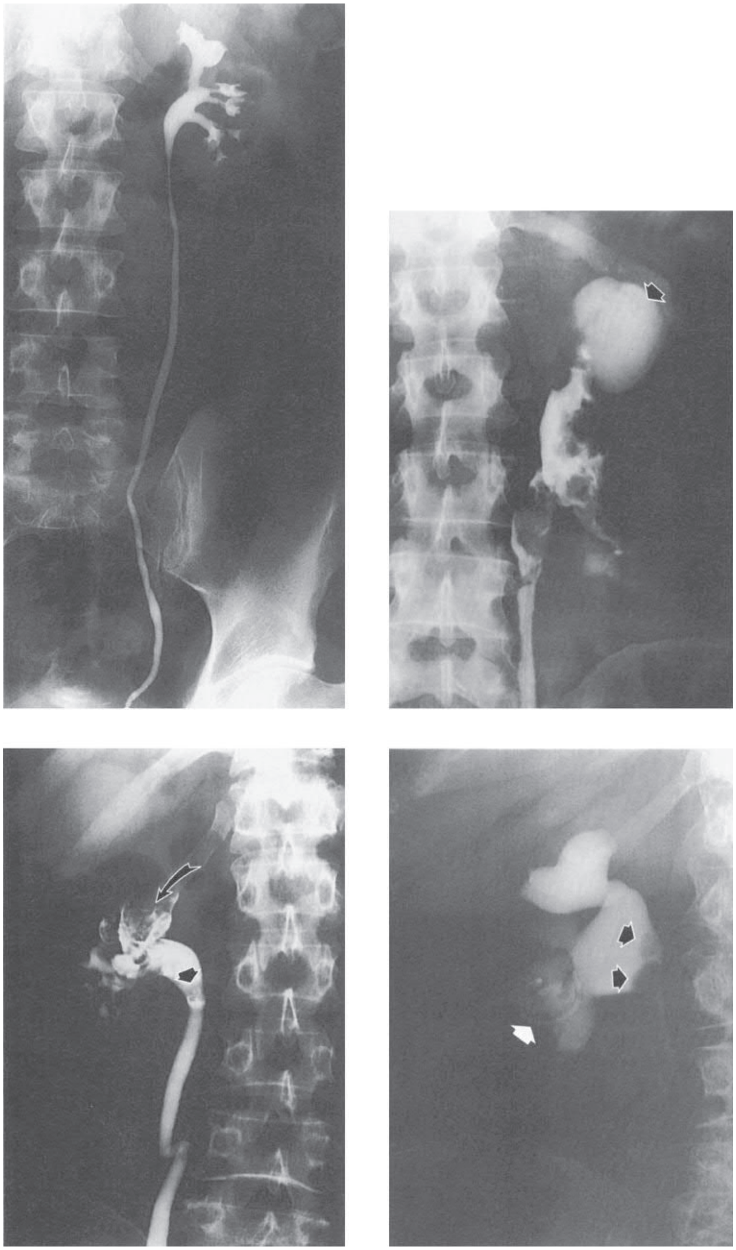
Retrograde Urograms

Retrograde urography is a minimally invasive procedure that requires cystoscopy and the placement of catheters in the ureters. A radiopaque contrast medium is introduced into the ureters or renal collecting structures through the ureteral catheters (Figures 6–7 and 6–8), and radiographs of the abdomen are taken. This study must be performed by a urologist or experienced interventional uroradiologist. Some type of local or general anesthesia should be used, and the procedure occasionally causes later morbidity or urinary tract infection.

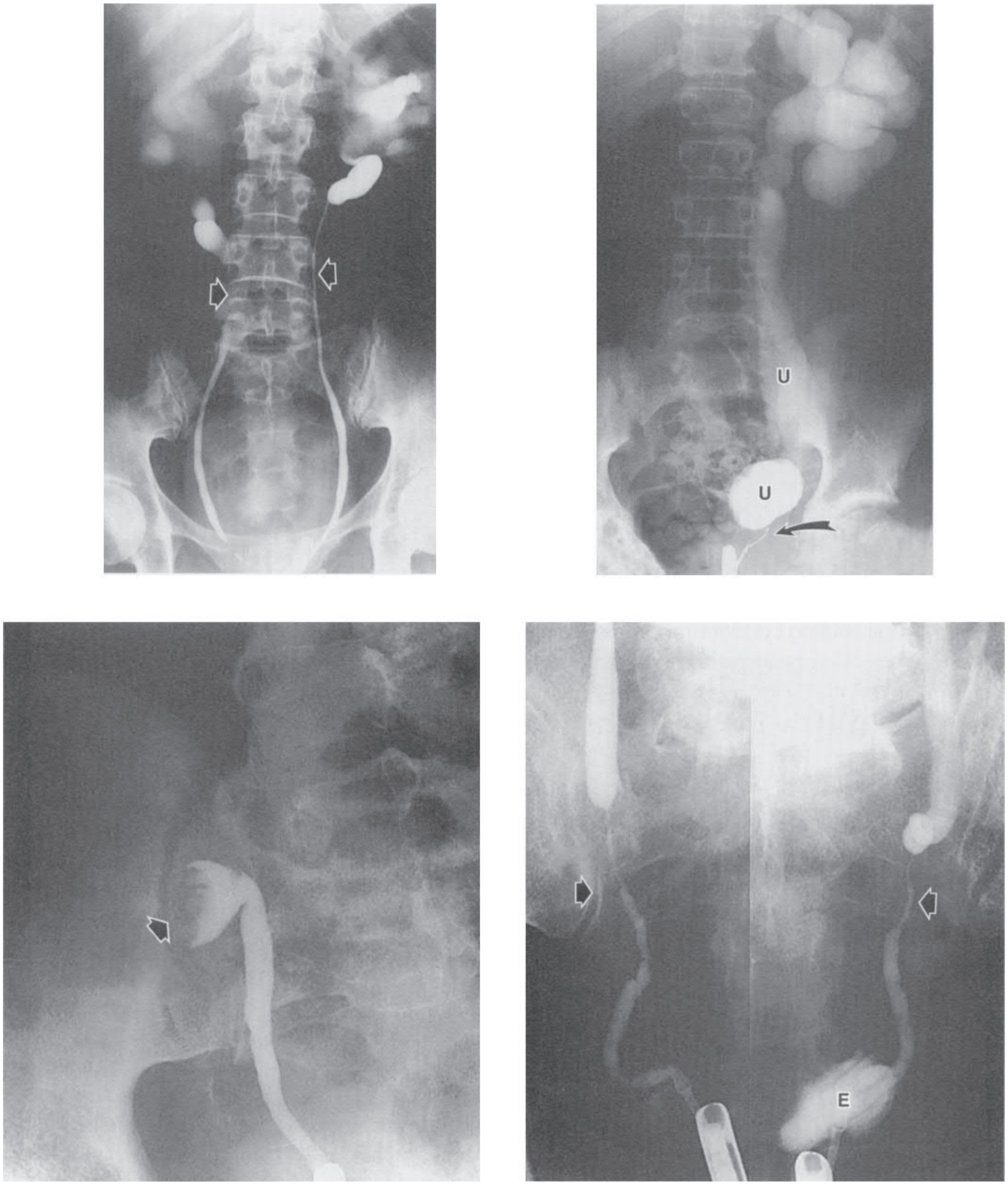
Retrograde urograms may be necessary if excretory urograms or CT urogram (CTU) are unsatisfactory, if the patient has a history of adverse reaction to intravenous contrast media, or if other methods of imaging are unavailable or inappropriate.

Percutaneous Urograms

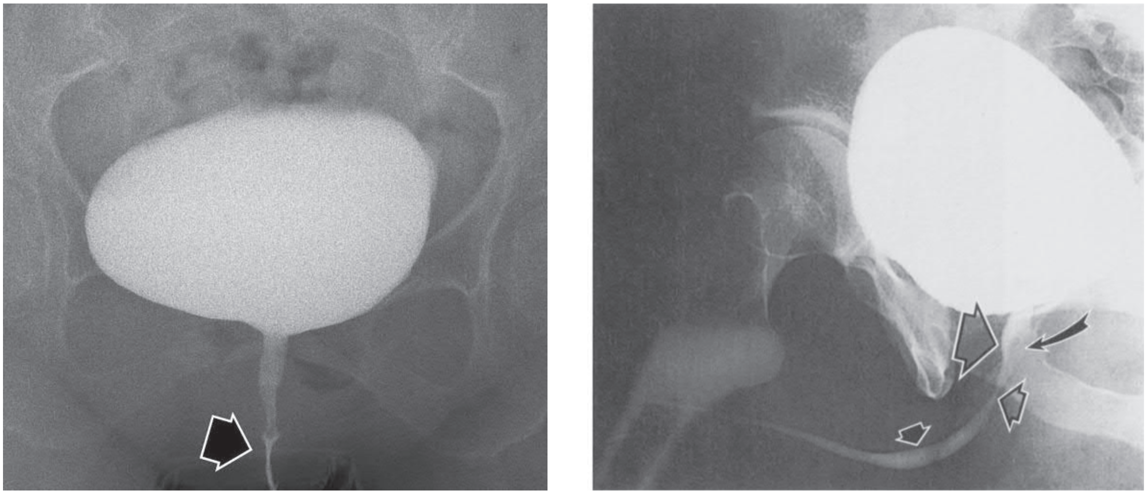
Outlining the renal collecting structures and ureters by percutaneous catheter is occasionally done when excretory or retrograde urography has failed or is contraindicated, or when there is a nephrostomy tube in place and delineation of the collecting system is desired. For antegrade studies, contrast medium is introduced either through nephrostomy tubes (nephrostogram) or by direct injection into the renal collecting structures via a percutaneous puncture through the patient's back. Percutaneous retrograde urograms of the upper urinary tract are made by retrograde injection of contrast medium through the opening of a skin ureterostomy or pyelostomy (skin ureterogram, skin urogram) or through the ostium of an interposed conduit, usually a segment of small bowel (loopogram).



▲ **Figure 6–7.** Retrograde urograms and nephrostograms; not all lower ureters are shown. ***Upper left:*** Normal retrograde urogram. Intrarenal collecting structures, pelvis, and ureter are normal. Adult male with microscopic hematuria and previous technically unsatisfactory excretory urogram. ***Upper right:*** Squamous cell carcinoma. Marked irregular filling defects involving calices, pelvis, and proximal ureter, with communicating abscess cavity in upper pole (*arrow*). Kidney also showed squamous metaplasia and contained calculi. A 51-year-old woman with 2-week history of left flank cellulitis and tenderness. ***Lower Left:*** Transitional cell carcinoma. Severe deformity with filling defects in right upper pole calices (*curved arrow*) and blood clots in lower calices and at ureteropelvic junction (*straight arrow*). A 65-year-old man with gross hematuria and right flank pain. ***Lower right:*** Fungus balls. Nephrostogram revealing two filling defects (*arrows*) in renal pelvis. Copious fungal matter aspirated through nephrostomy catheter. A 65-year-old diabetic woman who had undergone left nephrectomy, with percutaneous nephrostomy catheter (*white arrow*) for obstruction of right kidney.



▲ **Figure 6–8.** Abnormal retrograde urograms. ***Upper left:*** Idiopathic retroperitoneal fibrosis. Smooth narrowing of both midureters (*arrows*), with bilateral proximal ureterectasis and hydronephrosis. A 51-year-old woman with no urinary tract symptoms. ***Upper right:*** Functional ureteral obstruction. Obstruction was due to congenitally abnormal muscle arrangements in the affected very distal ureter (*curved arrow*). Pronounced hydronephrosis and dilatation of ureter (U) proximal to the short segment of abnormal ureter. A 13-year-old boy with repeated urinary tract infections. ***Lower left:*** Transitional cell carcinoma of the ureter. No contrast medium has passed beyond the large, bulky, right ureteral tumor (*arrow*). The ureteral widening below the tumor is distinctive and is sometimes referred to as the "champagne glass" sign (in this instance, the glass is tipped on its side). A 76-year-old man with nonfunctioning right kidney. ***Lower right:*** Ureteral constrictions secondary to extension of carcinoma of the colon. Bilateral distal ureteral narrowings (*arrows*) with upper tract obstruction. Composite of separate retrograde urograms (E = unintended extravasation about tip of left ureteral catheter). A 76-year-old man with cancer of the sigmoid colon.



▲ **Figure 6–9.** Normal voiding cystourethrograms. ***Left:*** Normal female bladder and urethra. Arrow indicates urethral meatus. A 31-year-old woman with voiding symptoms. ***Right:*** Normal male penile urethra. Large open arrow = prostatic urethra; small open arrow = membranous urethra; closed arrow = penile urethra; curved arrow = verumontanum. A 27-year-old man with vague right lower abdominal and testicular pain.

3. Cystography, voiding, cystourethrography, and urodynamics (Figures 6–9 to 6–12)—Direct instillation of contrast media into the urinary bladder (cystography) allows a more focused examination of the bladder. Contrast is usually instilled via a transurethral catheter, but when necessary it can be administered via percutaneous suprapubic bladder puncture. For urodynamic studies, pressure transducers are used within the bladder lumen and rectum for dynamic measurement of intraluminal and intra-abdominal pressures, respectively. Radiographs can be taken using standard overhead x-rays, or during fluoroscopy. **Voiding cystourethrograms** are radiographs of the bladder and urethra obtained during micturition. Cystography and cystourethrography are important radiologic techniques for detecting vesicoureteral reflux and may be used in the workup of patients with urinary stress incontinence. Both plain cystography and CT cystography (CT of the pelvis after the instillation of dilute contrast medium into the bladder) have been shown useful in the evaluation of traumatic bladder rupture or insufficiency in a postoperative setting (Patel et al, 2014; Lehnert et al, 2014).

4. Urethrography (Figures 6–13 to 6–15)—The urethra can be imaged radiographically by retrograde injection of radiopaque fluid, in antegrade fashion with voiding cystourethrography, or with voiding following EU. Retrograde urethrography is the preferred modality for the evaluation of male urethral injuries (Chapple et al, 2004). The antegrade technique is required when lesions of the posterior urethra, such as posterior urethral valves, are suspected; the retrograde technique is more useful for examining the anterior (penile) urethra. The urethra may also be evaluated by tailored MRI examinations using thin-section imaging with a small field of view. Urethral tumor or diverticula, for example, may be readily demonstrated with MRI (Ryu J and Kim B, 2001).

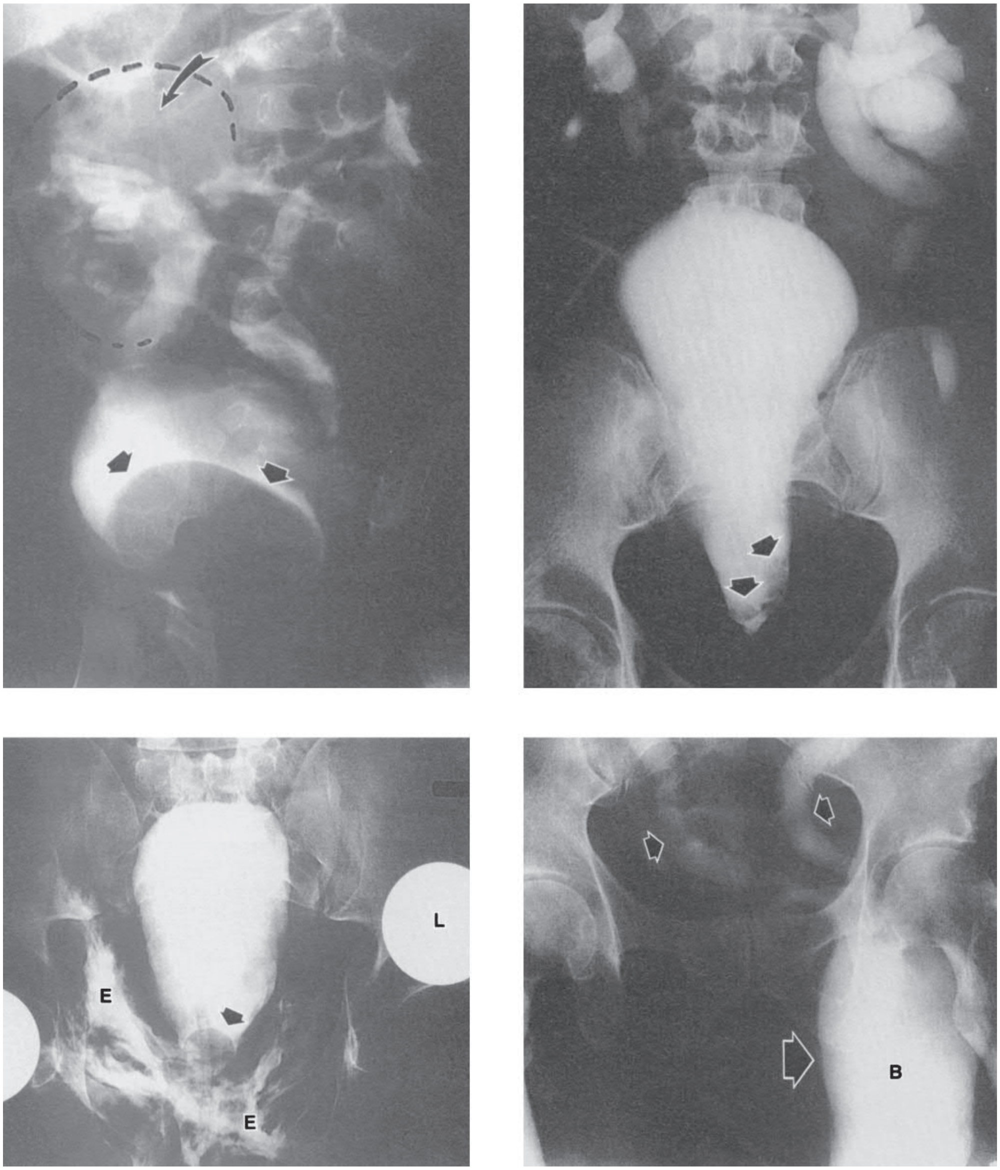
5. Vasography (Figure 6–16)—Vasoseminal vesiculography is most often used in the investigation of male sterility. The radiopaque contrast medium is introduced into the ductal system by direct injection into an ejaculatory duct following panendoscopy or, more commonly, by injection into the vas deferens after it has been surgically exposed through a small incision in the scrotal neck.

6. Lymphangiography—Lymphangiography has been largely abandoned and replaced by CT and MRI.

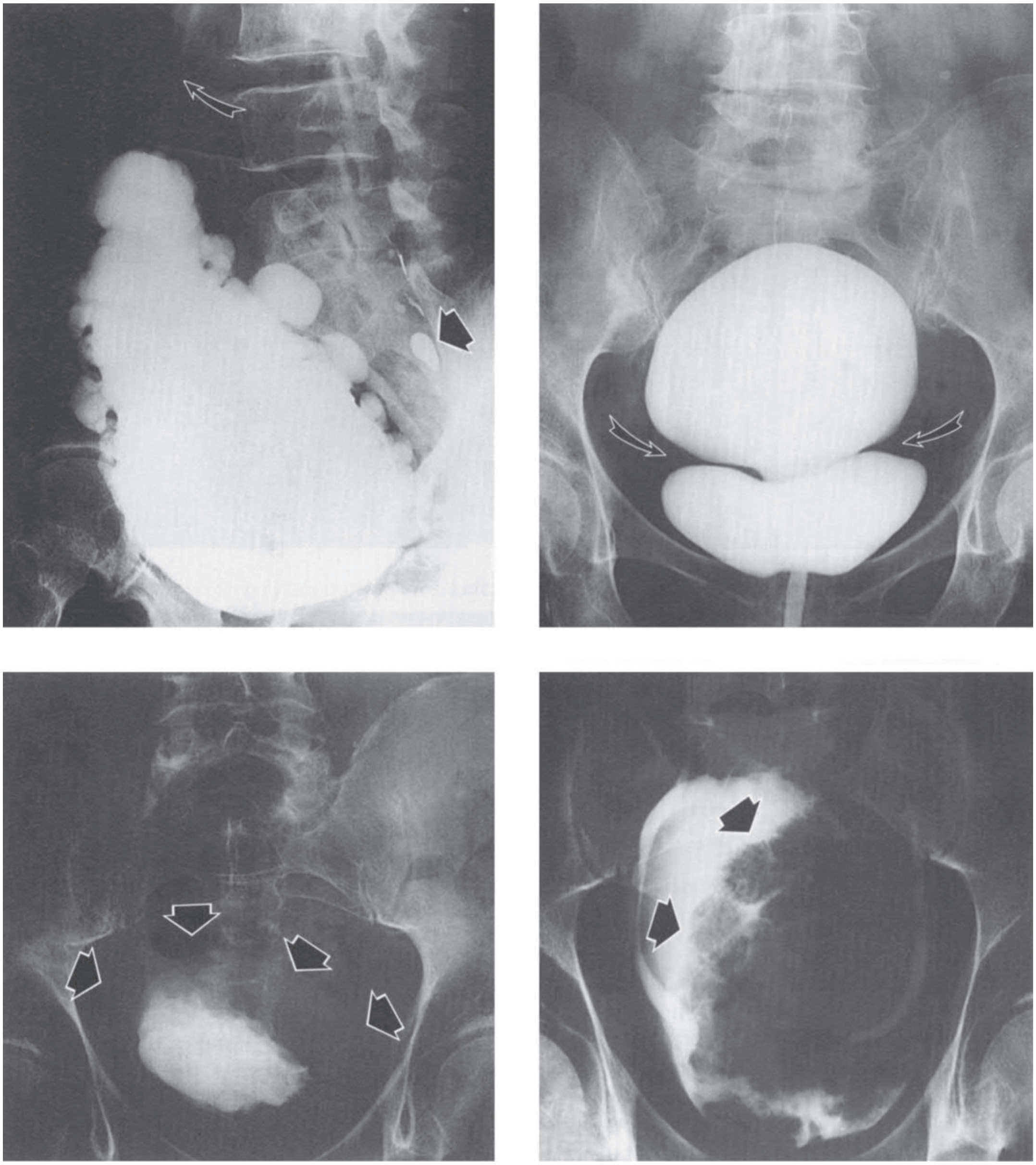
7. Angiography—Nearly 50 years after Seldinger described techniques for percutaneous arteriography, catheter angiography maintains a limited role in treatment of some urologic disorders but is being replaced by CT or MRI for diagnostic examinations. Although angiography is an established imaging technique with proven value and an acceptable incidence of complications and morbidity, it is moderately invasive and relatively expensive.

▶ Aortorenal and Selective Renal Arteriography (Figure 6–17)

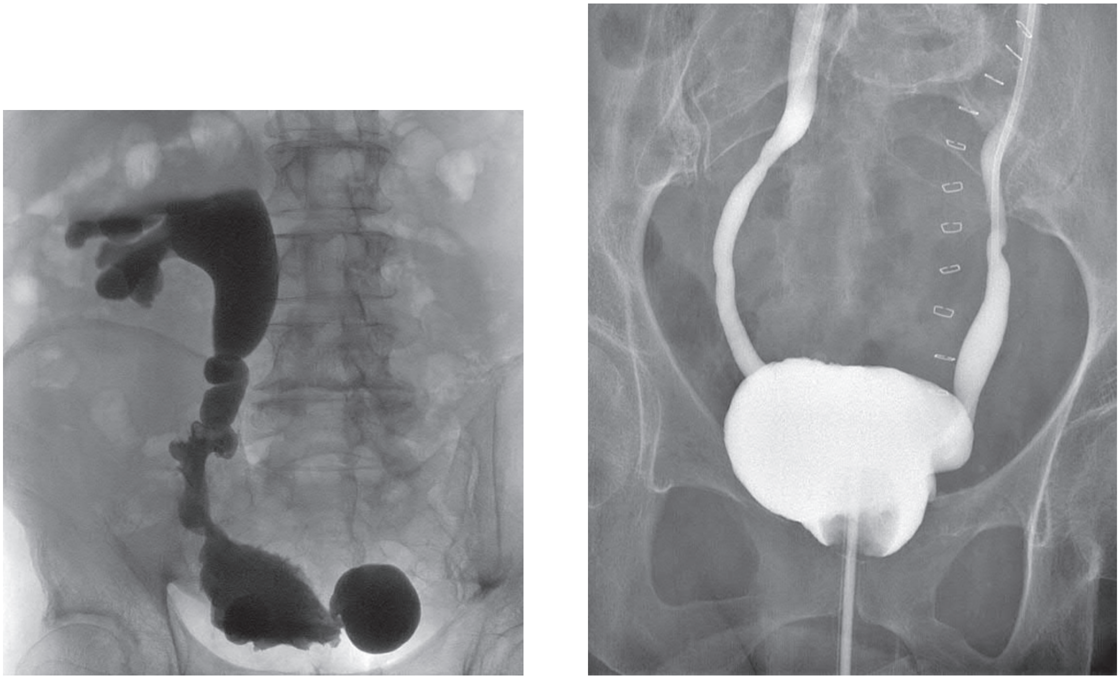
Conventional arteriographic studies are performed almost exclusively by percutaneous needle puncture and catheterization of the common femoral arteries. Rapid-sequence images are obtained during injection of nonionic contrast.



▲ **Figure 6–10.** Abnormal cystograms: retrograde cystograms or "cystograms" as part of excretory urogram studies. ***Upper left:*** Ectopic ureterocele. Giant ureterocele (*straight arrows*) to hydronephrotic, nonfunctioning upper portion (*curved arrow*) of duplex right kidney. A 9-month-old-girl with urinary tract infections. ***Upper right:*** Pelvic lipomatosis. Pear-shaped bladder and increased radiolucency of the pelvic soft tissues secondary to pelvic lipomatosis of severity sufficient to produce obstructive dilatation of the upper urinary tracts. Filling defects (*arrows*) at bladder base due to cystitis glandularis. A 62-year-old man with intermittent left flank pain. ***Lower left:*** Rupture of the membranous urethra. Pear-shaped bladder secondary to extraperitoneal extravasation (E) and perivesical hematoma. Inflated balloon of Foley catheter (*arrow*). A 41-year-old man with renal transplant, after a motor vehicle accident that resulted in pelvic bone fractures, separation of the sacroiliac joints, and dislocation of the left (L) but not the right hip prosthesis (patient has bilateral hip prostheses). ***Lower right:*** Bladder hernia. Bilateral obstructive ureterectasis (*small arrows*) secondary to remarkable herniation of the entire bladder (*large arrow*, B) into the inguinal region, A 5′5″, 225-lb, 53-year-old man with panniculus reaching to midthigh, complaining of difficulty voiding.



▲ **Figure 6–11.** Abnormal cystograms: retrograde cystograms or "cystograms" as part of excretory urogram studies. ***Upper left:*** Neurogenic bladder. This neurogenic bladder has a "Christmas-tree" shape, with gross trabeculation and many diverticula. Residual myelographic contrast medium in spinal canal (*straight arrow*). Right vesicoureteral reflux (*curved arrow*). A 70-year-old man with urinary incontinence. ***Upper right:*** Congenital "hourglass" bladder. Transverse concentric muscular band (*arrows*) separates upper and lower bladder segments, both of which contracted and emptied simultaneously and completely with voiding. A 66-year-old woman with urinary stress incontinence. ***Middle left:*** Hodgkin's disease of bladder. Global thickening of the bladder wall (*arrows*), more apparent on the left. A 54-year-old man with generalized Hodgkin's disease. ***Middle right:*** Papillary transitional cell bladder carcinoma. Huge (12-cm) cauliflower-like bladder mass (*arrows*) filling almost the entire bladder. "Cystogram" film of an excretory urogram in a 40-year-old man with recurrent bladder tumor. ***Lower left:*** Voiding cystourethrogram shows right-sided vesicoureteric reflux with marked dilatation of the ureter and hydronephrosis. ***Lower right:*** Voiding cystourethrogram shows bilateral vesicoureteral reflux. (*above and continued on next page*)



▲ **Figure 6–11.** (Continued)

Aortograms at the level of the renal vessels are followed by selective catheterization of renal arteries. CT and MR angiography involve peripheral injection of contrast media with breath hold rapid-sequence image acquisition through the targeted region of interest. CT angiography offers higher spatial resolution than magnetic resonance angiography (MRA) but carries the risks of radiation exposure and iodinated contrast usage.

Indications for renal arteriography include suspected renal artery stenosis (renovascular hypertension), vascular malformations, tumor embolization to minimize surgical blood loss or treat bleeding tumors, and trauma. Diagnostic renal angiography to demonstrate renal vascular anatomy is uncommon, as this information may be obtained noninvasively. Complications from conventional catheter angiography include bleeding at the puncture site, contrast allergy or nephrotoxicity, and renal or distal emboli.

Inferior Venacavography and Selective Venography (Figures 6–18 and 6–19)

The common femoral veins, or less commonly the internal jugular veins, are catheterized for angiography of the inferior vena cava and the renal and adrenal veins. Venography is rarely used today since the information can be obtained at cross-sectional imaging (CT or MRI) in almost all cases. Adrenal and renal venography is performed occasionally for venous sampling to localize hormone secretion in patients with indeterminate noninvasive imaging studies.

Miscellaneous Urologic Angiography

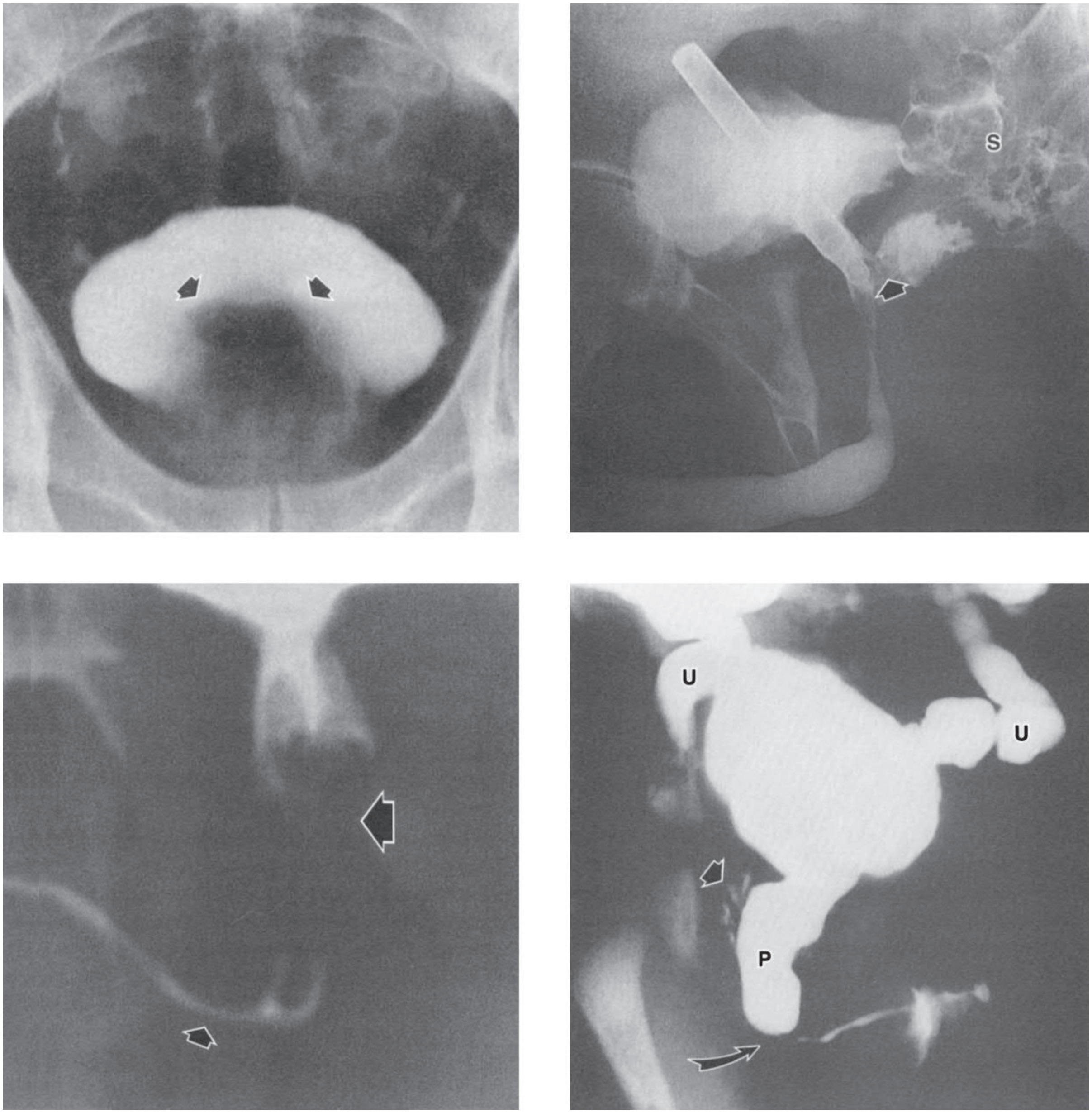
Although angiography has little or no value in examination of the ureter, bladder, adrenals, and prostate, angiograms of these structures may be indicated in certain clinical situations, in which case the studies are usually tailored to the clinical problem. In this era of multiple cross-sectional methods, these procedures are rarely used.

Although corpus cavernosograms are uncommon, they are filmed by direct injection of suitable contrast material into the corpora cavernosa of the penis. They can be useful in examining for Peyronie's disease or fibrosis, impotence, priapism, and traumatic penile lesions.

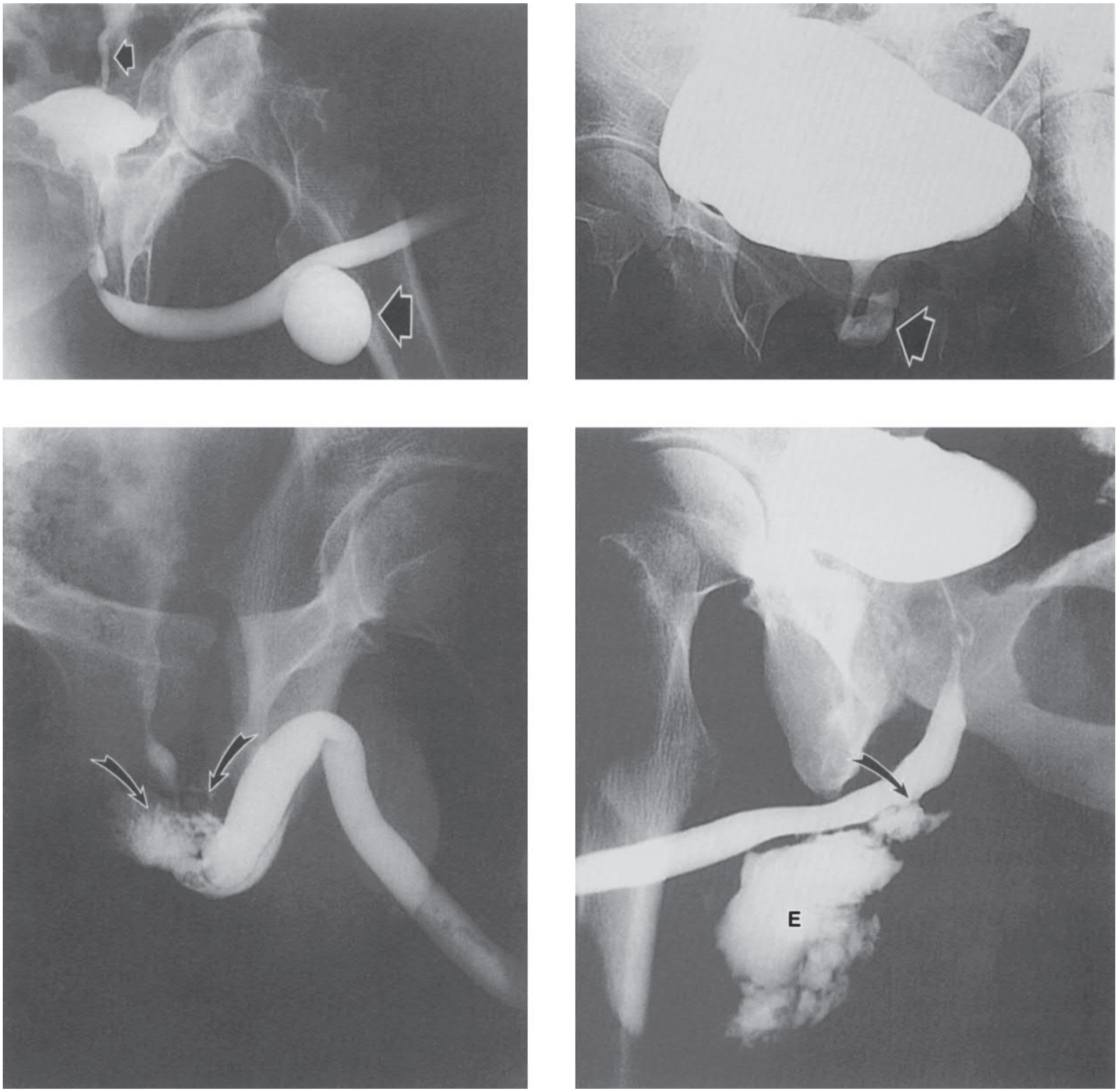
SONOGRAPHY (FIGURES 6–20 TO 6–26)

Basic Principles

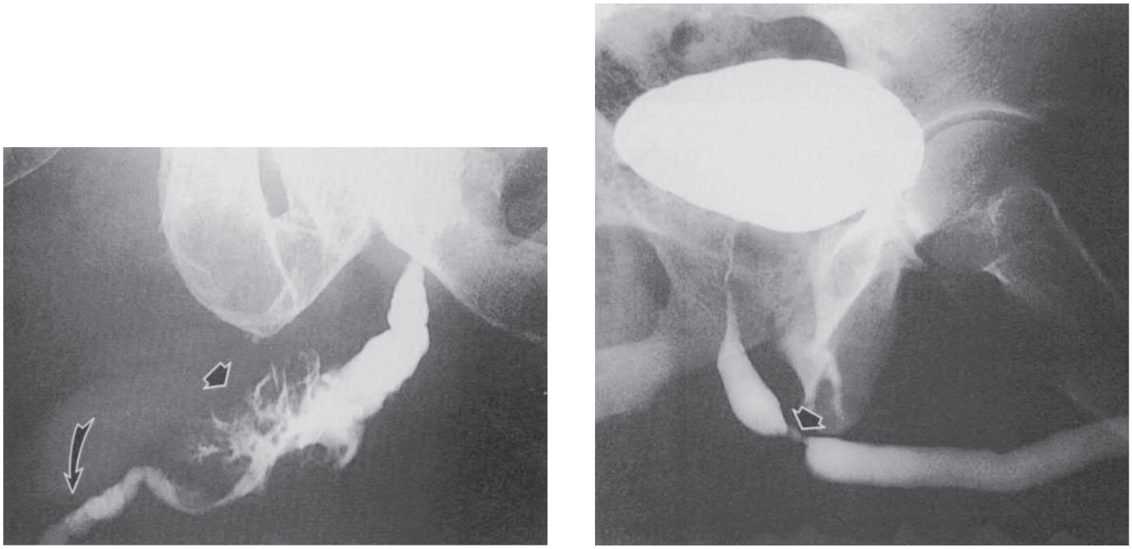
Sound is the mechanical propagation of pressure changes, or waves, through a deformable medium. A wave frequency of 1 cycle/s (cps) is called a **hertz** (Hz). Sound frequencies greater than 20 kHz are beyond the range of human hearing and are called **ultrasound**. Medical sonography uses ultrasound to produce images. The frequencies



▲ **Figure 6–12.** Abnormal prostate and posterior urethra: cystograms and urethrograms. ***Upper left:*** Benign prostatic hyperplasia. Gross enlargement of prostate gland producing marked elevation (*arrows*) of the bladder base. The bladder shows small diverticula and slight trabeculation. Excretory urogram (cystogram) in a 65-year-old man with history of obstructive voiding symptoms. ***Upper right:*** Foreign body (eyeliner pencil cover) lodged in bladder and prostatic urethra, with urethrorectal fistula. Radiopaque medium enters rectum and sigmoid colon (S) through fistula (*arrow*) from prostatic urethra. Retrograde urethrogram in a 43-year-old man. ***Lower left:*** Rhabdomyosarcoma of prostate. Lobulated filling defects (*large arrow*) encroaching on widened prostatic urethra. Voiding cystourethrogram in a 5-year-old boy with voiding difficulties. Penile urethra (*small arrow*). ***Lower right:*** Posterior urethral valves. Marked dilatation and elongation of prostatic urethra (P), with reflux into prostatic ducts (*straight arrow*) secondary to posterior urethral valves (*curved arrow*) with bilateral vesicoureteral reflux into dilated ureters (U). Voiding cystourethrogram in a 10-day-old boy.



▲ **Figure 6–13.** Abnormal anterior urethras: voiding cystourethrograms and retrograde urethrograms. ***Upper left:*** Voiding cystourethrogram in a 78-year-old man with a history of urethral diverticulum of unknown etiology. A 4-cm anterior urethral diverticulum (*large arrow*) and left vesicoureteral reflux (*small arrow*). ***Upper right:*** Urethral diverticulum in a woman. Large irregular diverticulum (*arrow*). Voiding cystourethrogram in a 51-year-old woman with voiding difficulties and suspected urethral stricture. ***Lower left:*** Ruptured urethra. Extravasation of contrast medium around the membranous urethra (*arrows*). Retrograde urethrogram in a 16-year-old boy in whom blunt perineal trauma was followed by bloody urethral discharge and inability to void. ***Lower right:*** Urethroscrotal fistula. Extravasation (E) into extraurethral tissues from fistula in bulbous urethra (*arrow*). Retrograde urethrogram in a 26-year-old man after end-to-end urethroplasty for stricture.



▲ **Figure 6–14.** Abnormal anterior urethras: retrograde urethrograms. ***Left:*** Urethral carcinoma. Filling of irregular sinus tracts and channels in a large epidermoid carcinoma of the bulbocavernous urethra (*straight arrow*). There are multiple thin transverse strictures of the penile urethra (*curved arrow*). A 75-year-old man with obstructive voiding symptoms and 30-year history of urethral strictures requiring dilatations. ***Right:*** Focal urethral stricture (*arrow*). Middle-aged man with obstructive voiding symptoms who denied previous urethritis.

commonly used in medical sonography range between 3.5 and 15 MHz.

Ultrasound waves for imaging are generated by **transducers**, devices that convert electrical energy to sound energy and vice versa. These transducers act as both sonic transmitters and detectors. Ultrasound images are reflection images formed when part of the sound that was emitted by the transducer bounces back from tissue interfaces to the transducer. The sound reflected by stationary tissues forms anatomic grayscale images. The sound reflected by moving structures has an altered frequency due to the Doppler effect. By determining the Doppler shift, vascular flow direction and velocity can be encoded graphically (**spectral Doppler**) or by color (**color Doppler**). A more sensitive method of detecting flow, called **power-mode Doppler**, is available on modern equipment. This technique displays the integrated power of the Doppler signal rather than the mean Doppler frequency shift. Direction or velocity of flow is not displayed in power mode. Newer intravascular microbubble contrast agents provide more exquisite imaging of vascularity, and their use will likely increase in coming years (Ascenti et al, 2007; Fan et al, 2008; Lu et al, 2015).

Ultrasound images are rapidly updated on a video display, giving an integrated cross-sectional anatomic depiction of the site studied. Individual frames may be frozen during an examination for motion-free analysis and recording, or cine images may be rapidly recorded as digital video.

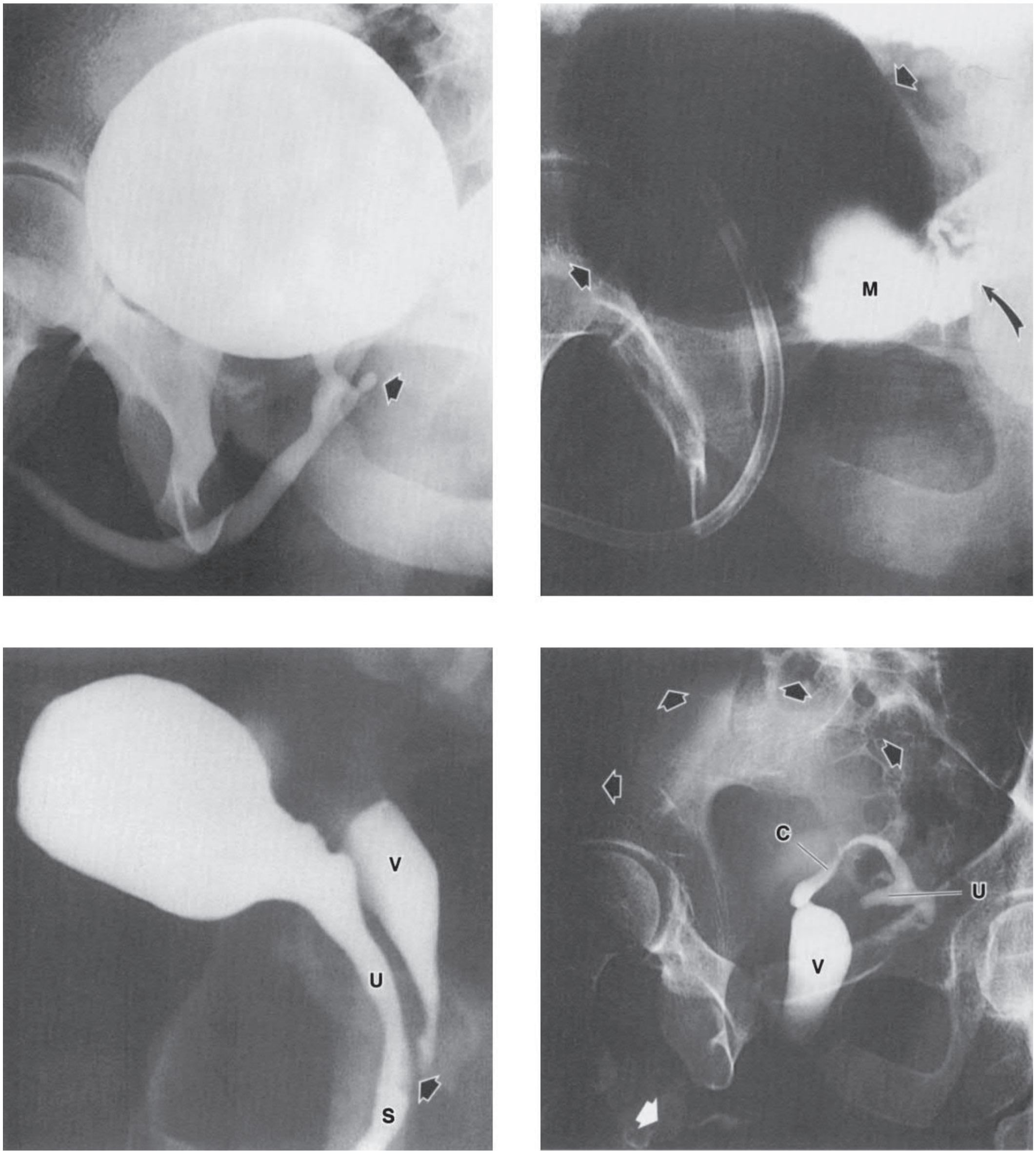
▶ Clinical Applications

Ultrasound is commonly used for the evaluation of the kidney, urinary bladder, prostate, testis, and penis.

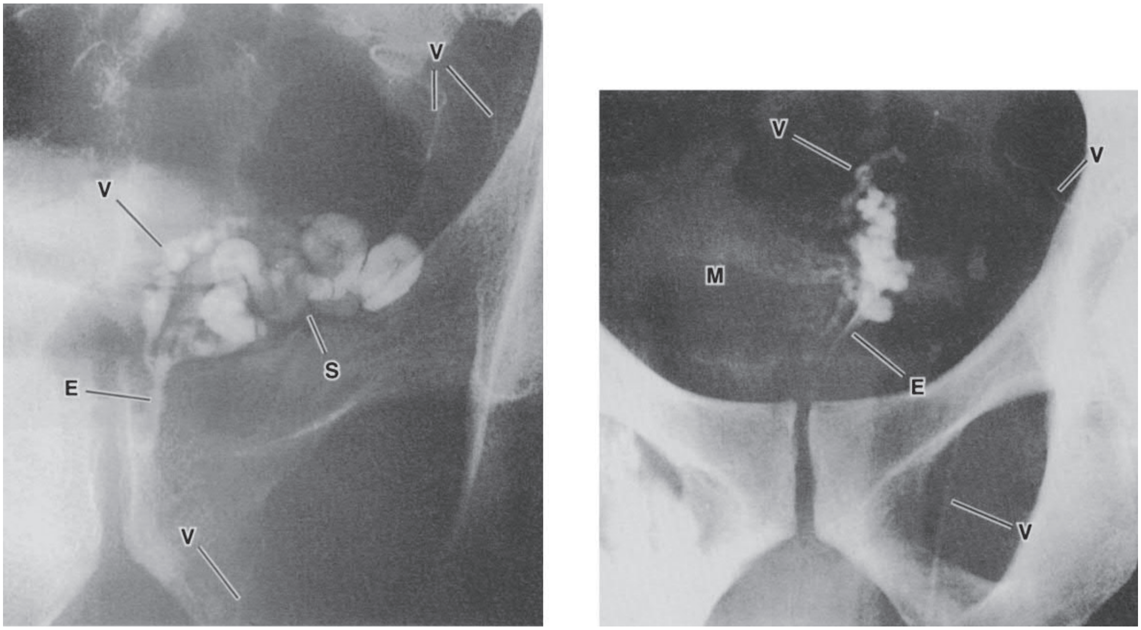
Ultrasound is useful for assessing renal size and growth. It is also helpful in triaging patients with renal failure. For example, small echogenic kidneys suggest renal parenchymal (medical) disease, whereas a dilated pelvocaliceal system indicates an obstructive, and potentially reversible, cause of renal failure.

Renal ultrasound is useful in detection and characterization of renal masses. Ultrasound provides an effective method of distinguishing benign cortical cysts from potentially malignant solid renal lesions. Since the most common renal lesion is a simple cortical cyst, ultrasound is a cost-effective method to confirm this diagnosis. Ultrasound may also be used to follow up mildly complicated cysts detected on CT, such as hyperdense cysts or cysts with thin septations.

The differential diagnosis for echogenic renal masses includes renal stones, angiomyolipomas, renal cortical



▲ **Figure 6–15.** Congenital genitourinary anomalies: voiding cystograms and retrograde urethrograms. ***Upper left:*** Utricle. Midline outpouching (*arrow*) from verumontanum between orifices of ejaculatory ducts, representing Müllerian duct cyst. ***Upper right:*** Gas cystogram combined with injection of utricle, oblique view. (M = grossly dilated utricle [Müllerian duct cyst]; *straight arrows* = bladder distended with air; *curved arrow* = coincident partial filling of left seminal vesicle and vas deferens.) A 34-year-old man with urgency, frequency, and suspected retrograde ejaculation. ***Lower left:*** Common urogenital sinus. Vagina (V) and urethra (U) join (at *arrow*) into a common urogenital sinus (S). Voiding cystourethrogram in a 3-week-old girl pseudohermaphrodite with ambiguous genitalia and congenital adrenal hyperplasia. ***Lower right:*** Male pseudohermaphrodite. Bladder is distended with urine (*black arrows*). Retrograde urethrogram via hypospadiac meatus has fortuitously and selectively filled with contrast medium an extensive Müllerian duct remnant consisting of vagina (V), cervix and cervical canal (C), and retroverted uterus (U). Residual contrast medium in hypoplastic anterior urethra (*white arrow*). A 27-year-old man with small external genitalia, hypospadias, and perineal pain.



▲ **Figure 6–16.** Vasoseminal vesiculography (vasography). ***Left:*** Normal left vasoseminal vesiculogram (V = vas deferens; S = seminal vesicle; E = ejaculatory duct). A 40-year-old man with hypospermia. ***Right:*** Seminal vesiculitis. Bilateral vasogram. Mass (M) produced by the swollen, nonfilling right seminal vesicle has displaced both ejaculatory ducts (E) toward the left and indented the medial aspect of the proximal left seminal vesicle and vas deferens (V). A 33-year-old man with painful ejaculations after repair of right varicocele.

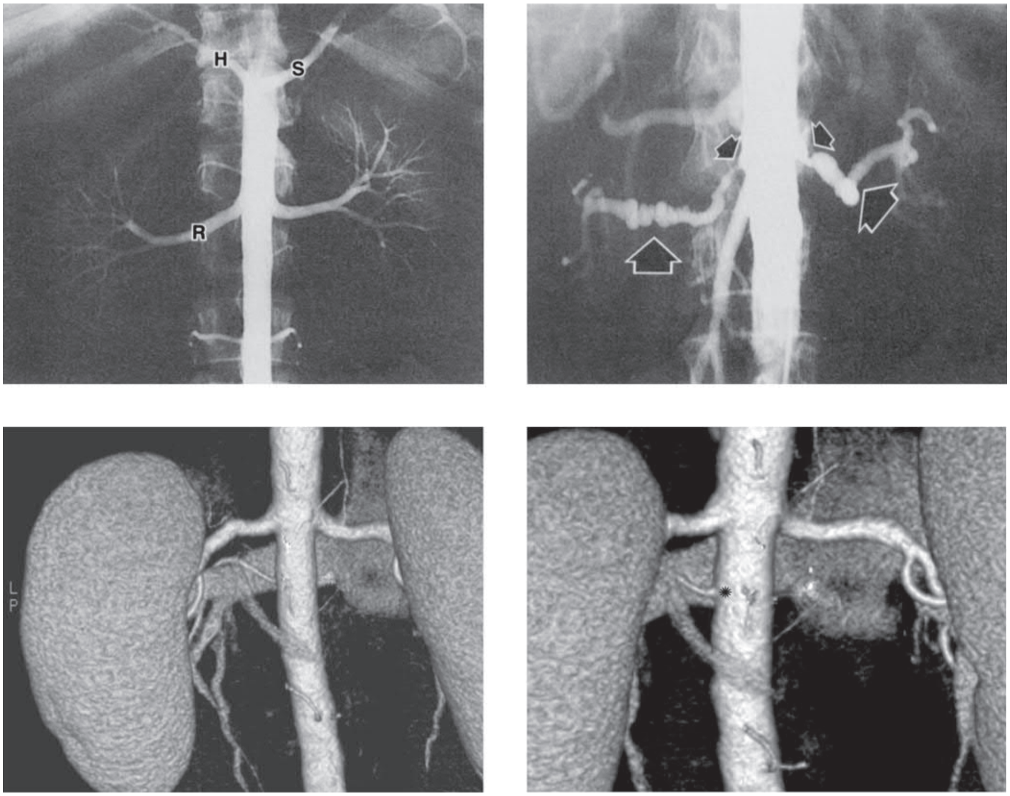
neoplasms (including carcinoma), and, less commonly, abscesses and hematomas. All echogenic renal masses should be correlated with clinical history and, if necessary, confirmed with another imaging modality or follow-up ultrasound. Thin-section CT showing fat within the renal lesion characterizes it as a benign angiomyolipoma, and no further investigation is required. Echogenic lesions smaller than 1 cm are more difficult to characterize by CT owing to partial-volume averaging; in the correct clinical setting, follow-up ultrasound rather than repeat CT may be more useful.

Doppler sonography is useful for the evaluation of renal vessels, vascularity of renal masses, and complications following renal transplant. It can detect renal vein thrombosis, renal artery stenosis, and ureteral obstruction prior to the development of hydronephrosis, arteriovenous fistulas, and pseudoaneurysms. Perinephric hematoma following trauma as well as fluid collections following renal transplantation, extracorporeal shockwave lithotripsy, or acute obstructions are reliably detected by ultrasound.

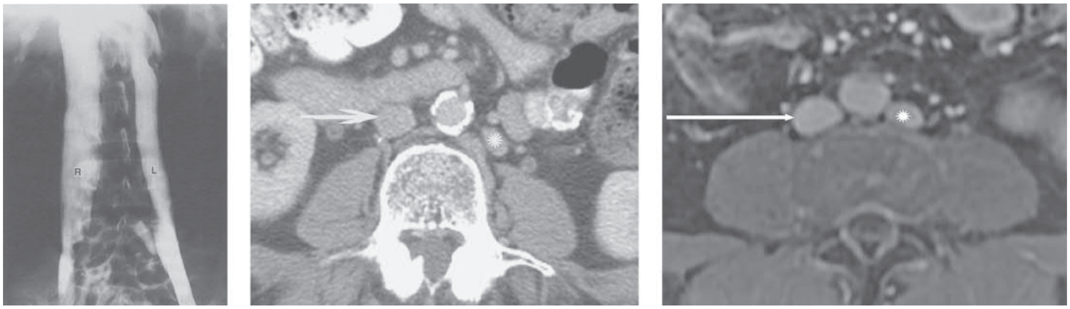
Developments in other imaging modalities have decreased the use of ultrasound in several clinical scenarios. Most patients with suspected renovascular hypertension are evaluated with CTA or MRA rather than Doppler ultrasonography. Unenhanced helical low-dose CT is now the initial procedure of choice for the evaluation of the patient with acute flank pain and suspected urolithiasis. Helical CT also has the potential for identifying other causes of flank pain such as appendicitis and diverticulitis. For the evaluation of hematuria, recent studies indicate that CT (or CTU) is the preferred modality (Cowan, 2012). A balance between optimizing imaging quality and minimizing radiation exposure is advocated.

Applications of bladder sonography include assessment of bladder volume, wall thickness, and detection of bladder calculi and tumors. The suprapubic transabdominal approach is most commonly used. The transurethral approach during cystoscopy has been recommended for tumor detection and staging.

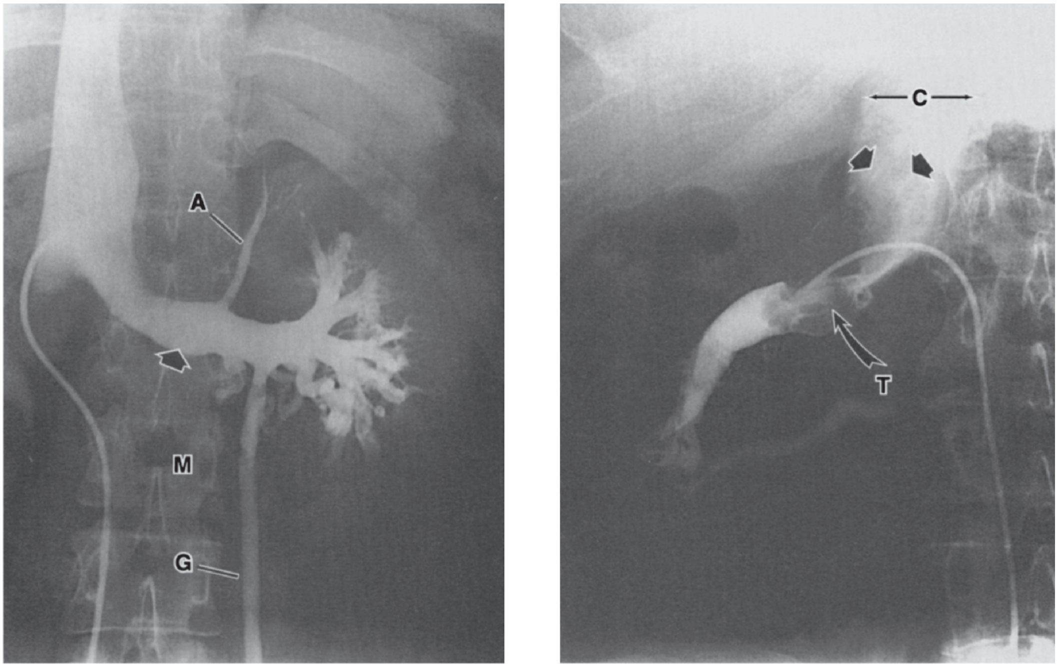
Ultrasound examination of the testis and scrotum is performed with a high-frequency transducer (10–15 MHz) for excellent spatial resolution. The addition of color and spectral Doppler sonography provides simultaneous display of morphology and blood flow. Sonography is highly accurate in differentiating intratesticular from extratesticular disease and in the detection of intratesticular pathology. Ultrasound is commonly used to evaluate acute conditions of the scrotum. It can distinguish between inflammatory processes,



▲ **Figure 6–17.** Angiography: aortorenal arteriography. ***Upper left:*** Normal abdominal aortogram. The aortic catheter is hidden by the opacified normal aorta. Right (R) and left renal arteries and branches are well shown, as are the splenic (S) and hepatic (H) arteries arising from the celiac axis. The superior mesenteric artery is superimposed over the aortic silhouette and is not visible here. A 28-year-old healthy woman potential kidney donor. ***Upper right:*** Bilateral renal artery stenoses. Typical angiographic appearance and location of stenoses caused by atherosclerosis (*small arrows*) and fibromuscular dysplasia (*large arrows*). A 58-year-old woman with abdominal bruits and a 16-year history of hypertension. ***Lower left:*** 3D coronal CT angiography image demonstrates an inferior accessory left renal artery (posterior view). ***Lower right:*** The left accessory renal artery origin (*asterisk*) is better demonstrated rotating the model in the axial plane. A 65-year-old man undergoing preoperative evaluation for laparoscopic partial nephrectomy.



▲ **Figure 6–18.** Angiography: inferior venacavography. ***Left:*** Double inferior vena cava (R, L). Persistent left supracardinal vein anomaly. A 23-year-old man after orchiectomy for testicular teratocarcinoma. ***Middle:*** Example of duplicated IVC on IV contrast-enhanced axial CT. Normal IVC (*arrow*) and duplicated IVC (*asterisk*). ***Right***: Example of duplicated IVC on IV contrast-enhanced axial T1-weighted fat-saturated MRI. Normal IVC (*arrow*) and duplicated IVC (*asterisk*).



▲ **Figure 6–19.** Angiography: renal venography. ***Left:*** Normal left renal vein. On the left side, the adrenal (A) and gonadal (G) veins enter the renal vein (*arrow*). (M = radiographic localization marker.) Young woman with proteinuria. ***Right:*** Tumor thrombus. Upper margin (*straight arrows*) of filling defect of the renal vein tumor thrombus (T) that extends into the vena cava (C). A 68-year-old man with gross hematuria from adenocarcinoma of the right kidney.

inguinal hernias, and acute testicular torsion (Hart et al, 2008; Sparano et al, 2008). Epididymitis not responding to antibiotics within 2 weeks should be investigated further with scrotal ultrasonography.

Advantages and Disadvantages

The main advantages of ultrasound are ease of use, high patient tolerance, noninvasiveness, lack of ionizing radiation, low relative cost, and wide availability. Disadvantages include a relatively low signal-to-noise level, tissue nonspecificity, limited field of view, and dependence on the operator's skill and the patient's habitus.

COMPUTED TOMOGRAPHY SCANNING (FIGURES 6–27 TO 6–33)

Basic Principles

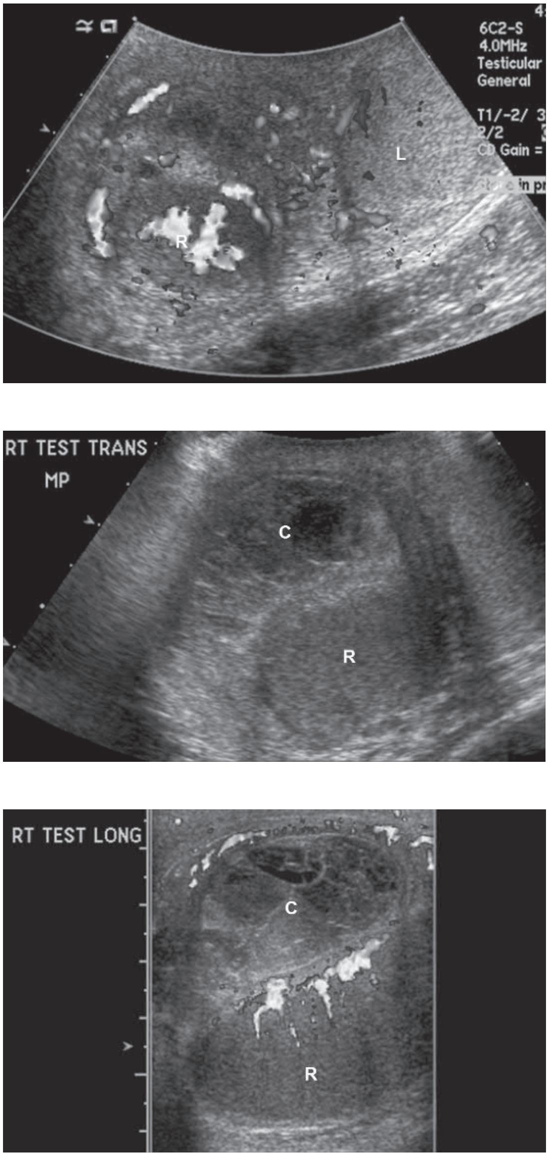
In CT scanning, a thin, collimated beam of x-rays is passed through the patient and captured by an array of solid-state or gas detectors.

The interconnected x-ray source and detector system are rapidly rotated in the gantry around the recumbent patient. Computers integrate the collected x-ray transmission data to reconstruct a cross-sectional image (tomogram).

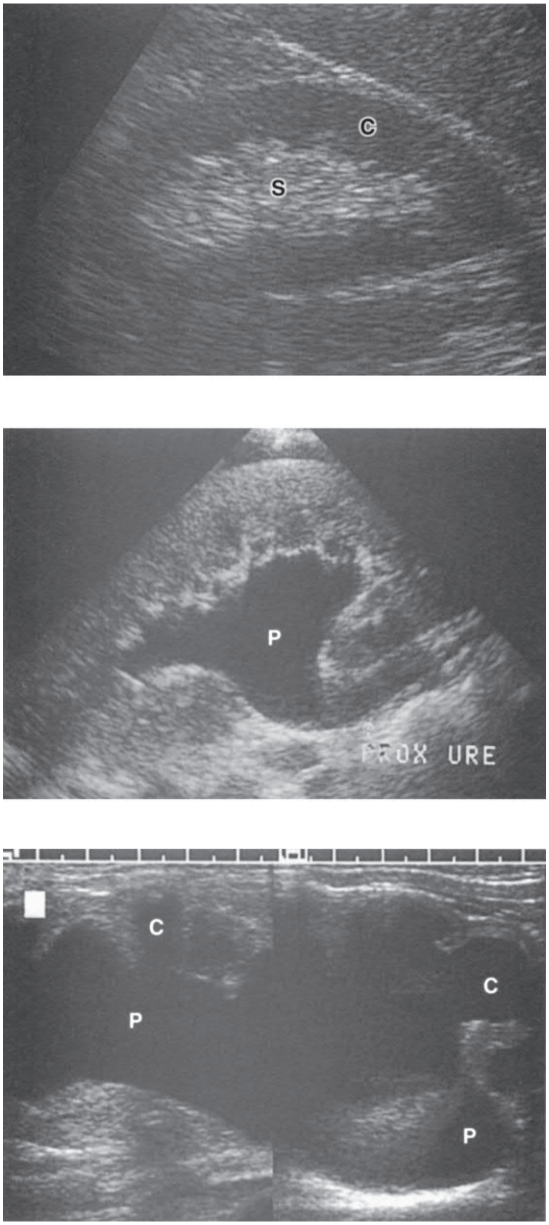
Spiral (or helical) CT uses a slip-ring gantry that rotates continuously while the patient moves constantly through the collimated x-ray beam. Spiral CT technology affords the ability to image during specific phases of contrast bolus enhancement, including the ability to perform CT angiography, and allows improved image reformations. Multidetector, or multislice, helical CT scanners have an array of multiple rows of detectors in a helical scanner such that multiple scan images can be acquired per gantry rotation, and as a by-product thinner sections and higher resolution can be achieved. Such systems are optimally paired with powerful computer workstations so that high-quality three-dimensional (3D) and multiplanar reformations can be quickly generated and analyzed.

Clinical Applications

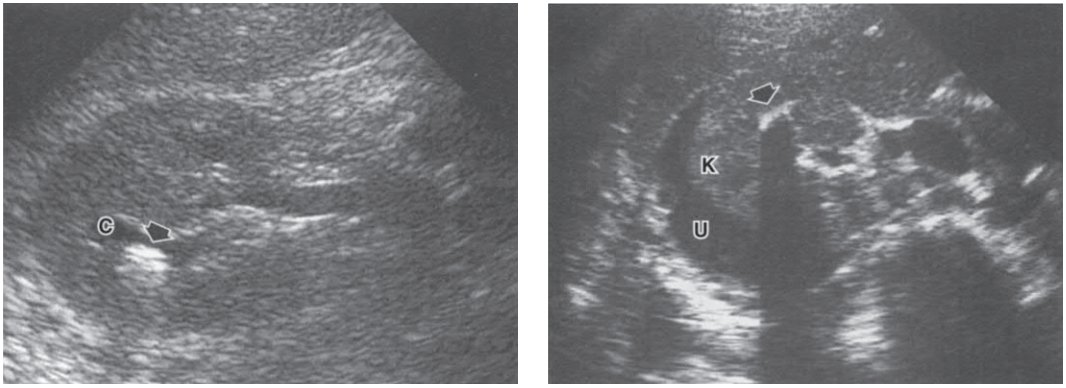
Renal CT is most commonly used in the evaluation of acute flank pain, hematuria, and renal infection (search for abscesses) or trauma and in the characterization and staging of renal neoplasm. CT evaluation of renal anatomy



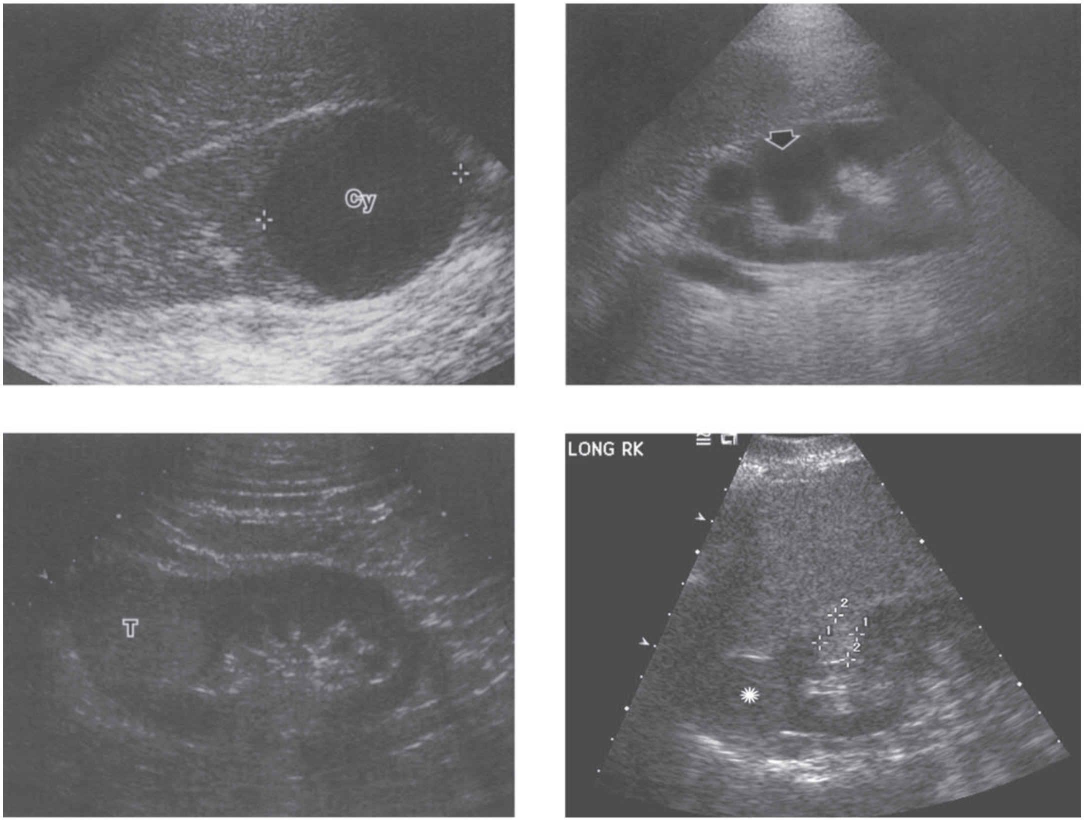
▲ **Figure 6–20.** A 67-year-old man recently hospitalized for urosepsis. ***Upper:*** Transverse color Doppler image of the right (R) and left (L) testicles reveals right-sided hyperemia with associated hypoechoic echotexture and surrounding hypoechoic mass. ***Middle:*** Transverse gray-scale right hemiscrotal image confirms hypoechoic right testicle (R) and extratesticular complex collection within the epididymal tail (C). ***Lower:*** Color Doppler confirms lack of flow within the complex collection. Pathology confirmed chronic granulomatous orchitis, epididymitis, and periorchitis.



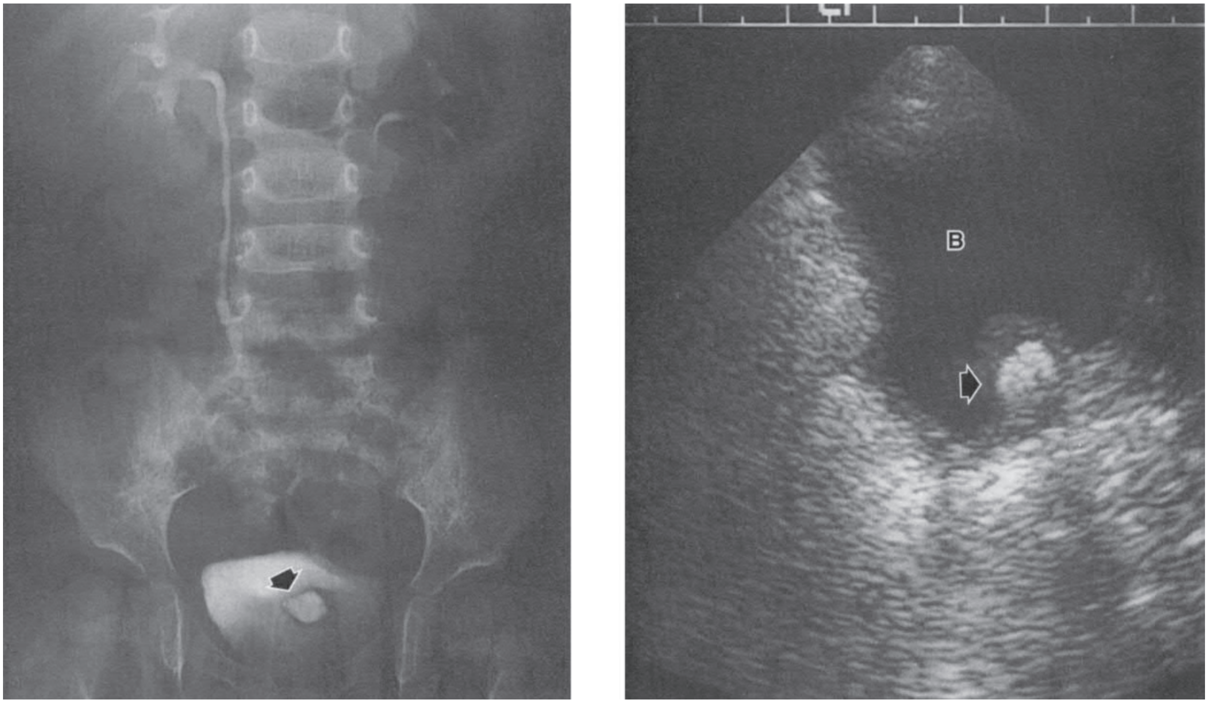
▲ **Figure 6–21.** Sonography of the kidney. ***Upper:*** Normal kidney. Renal cortex (C), normal renal sinus echoes (S). ***Middle:*** Moderate hydronephrosis and hydroureter; dilated renal pelvis (P). Dilated proximal ureter (proxure). ***Lower:*** Severe hydronephrosis of the transplanted kidney, compound sagittal scans, dilated clubbed calices (C), dilated renal pelvis (P).



▲ **Figure 6–22.** Renal calculus and the consequences of obstruction as detected by sonography. ***Left:*** Transverse scan of the right kidney showing calicectasis (C) and renal calculus (*arrow*). ***Right:*** Acute obstruction of the right kidney (K) with spontaneous urine (U) extravasation into the perirenal space. Renal calculus (*arrow*).



▲ **Figure 6–23.** Sonography of renal neoplasms. ***Upper left:*** Simple renal cyst (Cy) demonstrating sharp interfaces toward the renal parenchyma, no internal echoes, and increase through transmission. ***Upper right:*** Complex renal cyst (*arrow*) with lobulated margins and thick wall. ***Lower left:*** Solid tumor (T) in upper pole of left kidney with increased echogenicity relative to adjacent renal parenchyma. Pathology was oncocytoma. ***Lower right:*** Solid renal tumor (*asterisk*) in the right kidney (K) with separate hyperechoic interpolar partially exophytic mass. The interpolar mass represented a known angiomyolipoma, while the upper pole mass represented renal cell carcinoma.



▲ **Figure 6–24.** Sonography with comparative study. Film from IVP (***left***) and transabdominal ultrasound (***right***) of the urinary bladder in a patient with duplication of the left kidney, ectopic ureterocele, and a calculus (*arrow*) within it. Urinary bladder (B).

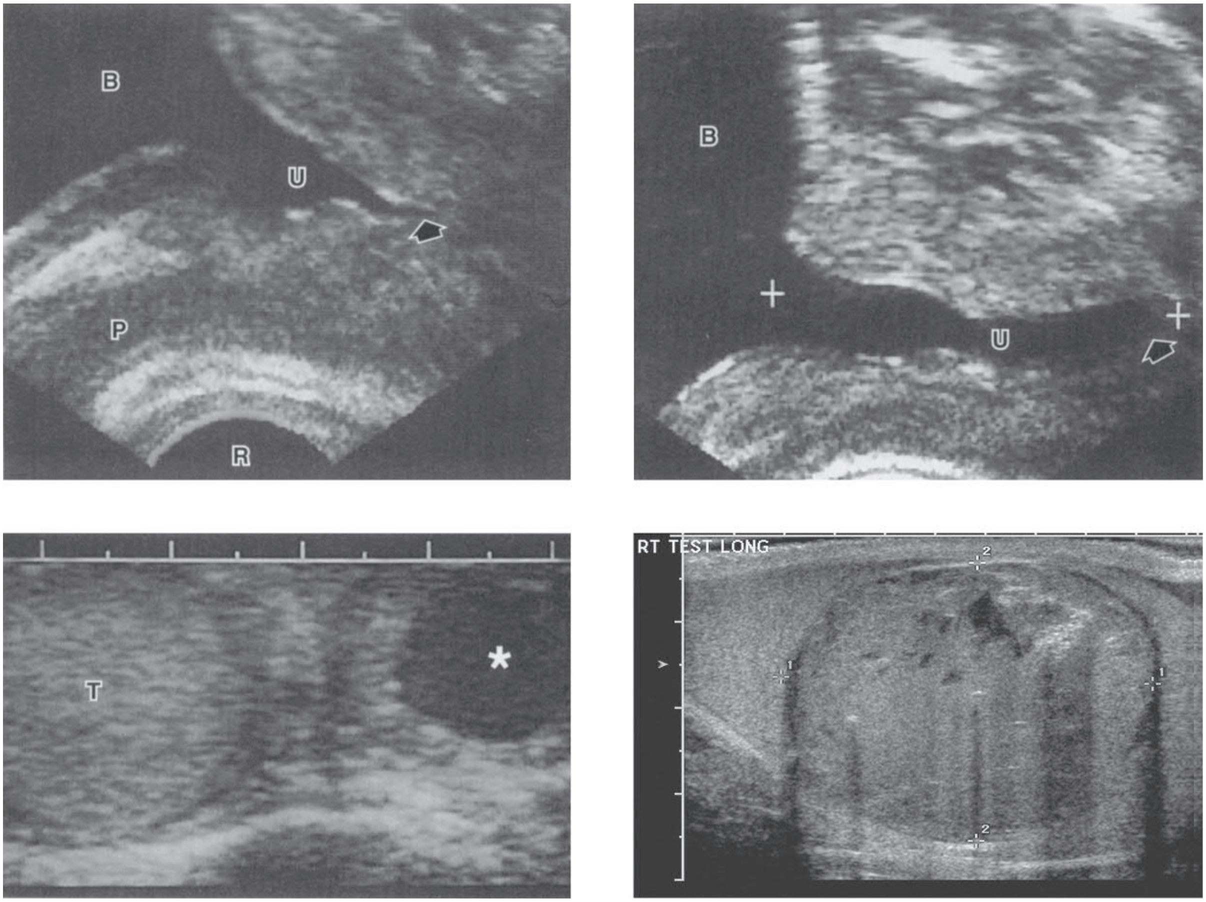
and pathology generally requires intravenous injection of iodinated contrast media; noncontrast scans are needed, however, when renal or perirenal calcification, hemorrhage, or urine extravasation is suspected, since scans obtained after the administration of contrast media may mask these abnormalities. Also, pre- and postcontrast scans are required to determine whether a mass is solid or cystic.

Contrast medium is usually administered as a rapid intravenous bolus. Using a bolus injection and multiphasic multidetector CT, renal arterial opacification is followed immediately by enhancement of the cortex. A nephrogram phase with medullary enhancement is reached within 60 seconds. Excretion of contrast material into the collecting structures can be expected within 2–3 minutes after initiation of contrast administration, depending on the renal excretory function.

Although CT can detect ureteral tumors, the current role of CT in evaluation of the ureters is predominantly for tumor staging and evaluation of the cause and level of obstruction. Helical low-dose CT without oral or intravenous contrast is the preferred imaging modality for patients with renal colic or suspected urolithiasis (Figure 6–32).

In evaluation of the urinary bladder, CT is used primarily in staging bladder tumors and diagnosing bladder rupture following trauma (Shin et al, 2007) and in the postoperative setting. Performing CT after filling the bladder with dilute contrast medium (CT cystography) improves the sensitivity of this modality for detecting tumors and bladder rupture. For prostate diseases, CT is used for detection of lymphadenopathy, for gross extraprostatic tumor extension, and to delineate prostatic abscesses. CT is used for detection of the abdominal location of suspected undescended testes, for staging of testicular tumors, and in the search for nodal or distant metastasis.

The addition of delayed CT imaging 10–15 minutes after intravenous contrast-enhanced CT shows high sensitivity and specificity in characterizing adrenal lesions. Benign adenomas, including lipid poor adenomas, show brisk contrast washout. CTA or MRA are replacing

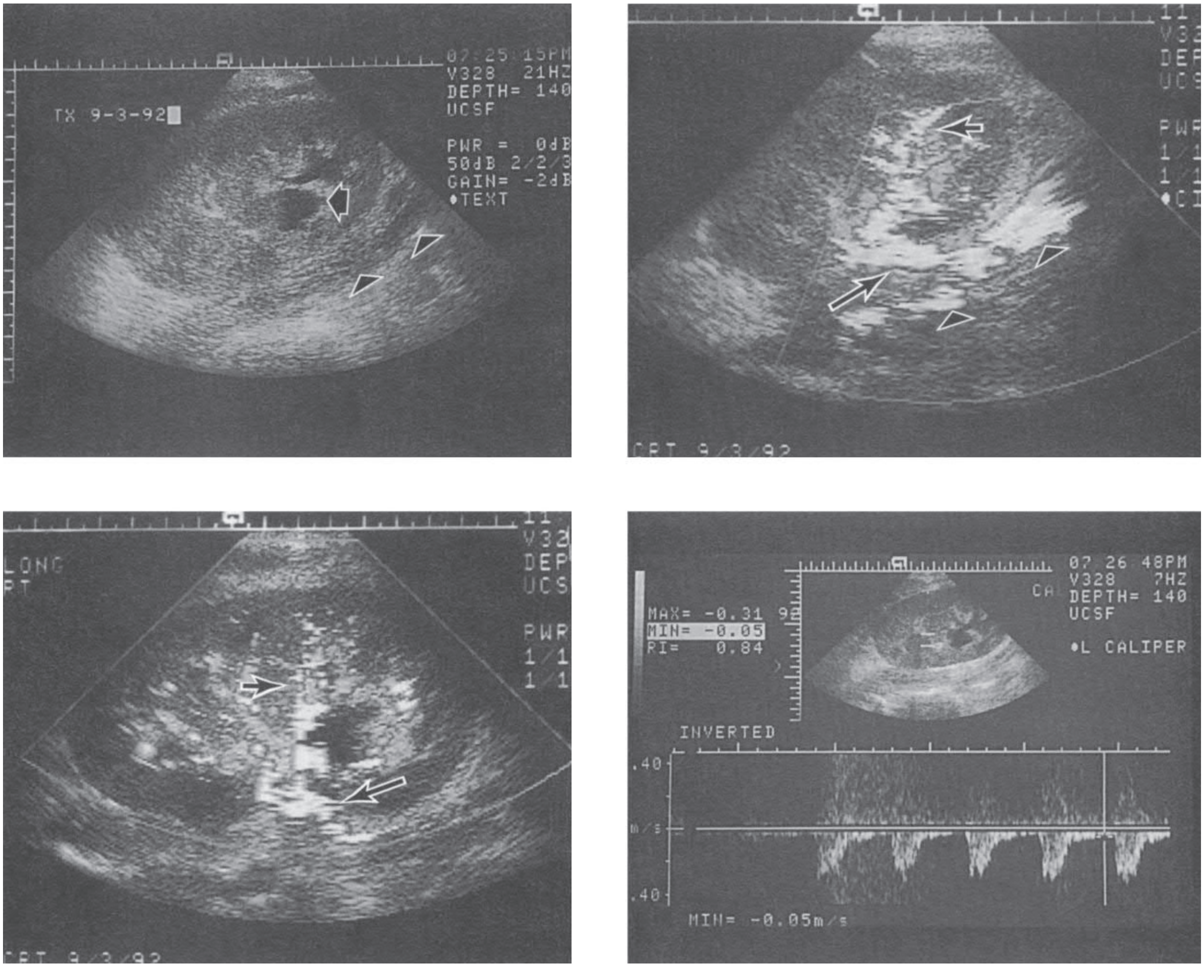


▲ **Figure 6–25.** The use of transrectal ultrasound in the evaluation of the prostatic urethra. ***Upper left:*** Sonographic appearance of the prostatic urethra (U) following transurethral resection as seen on transrectal ultrasound in the sagittal plane of scanning. Urinary bladder (B). The urethra (U) is dilated to the level of the verumontanum (*arrow*). Peripheral zone (P), rectum (R). ***Upper right:*** The prostatic urethra (U) is dilated to the level to the membranous urethra (*arrow*). Urinary bladder (B). The cursors are placed to measure the length of the prostatic urethra. ***Lower images:*** Examples of testicular ultrasound. ***Lower left:*** The right testis (T) is normal. There is a hypoechoic lesion within the left testis (*asterisk*). At surgery, it was a seminoma. ***Lower right:*** A large mixed solid and cystic intratesticular mass with foci of echogenic calcifications. Benign epidermoid cyst. This mass did not show the concentric lamellation sometimes associated with epidermoid cysts. Ultrasound cannot always differentiate epidermoid cysts from malignant germ cell neoplasms.

conventional angiography for diagnostic examinations. New, dual-energy CT using dual or alternating sources of scan energy offers added benefits for postcontrast evaluation and allows virtual noncontrast imaging. Dual-energy CT will likely play an increasing role in evaluation for incidental renal (Brown et al, 2009; Graser et al, 2009) and adrenal (Mileto et al, 2015) masses, as well as in evaluation for urolithiasis, including stone composition determination (eg, for urate stones) (Eiber et al, 2012; Boll et al, 2009; Graser et al, 2008; Primak et al, 2007).

Advantages and Disadvantages

The main advantages of CT include a wide field of view, the ability to detect subtle differences in the x-ray attenuation properties of various tissues, good spatial resolution, anatomical



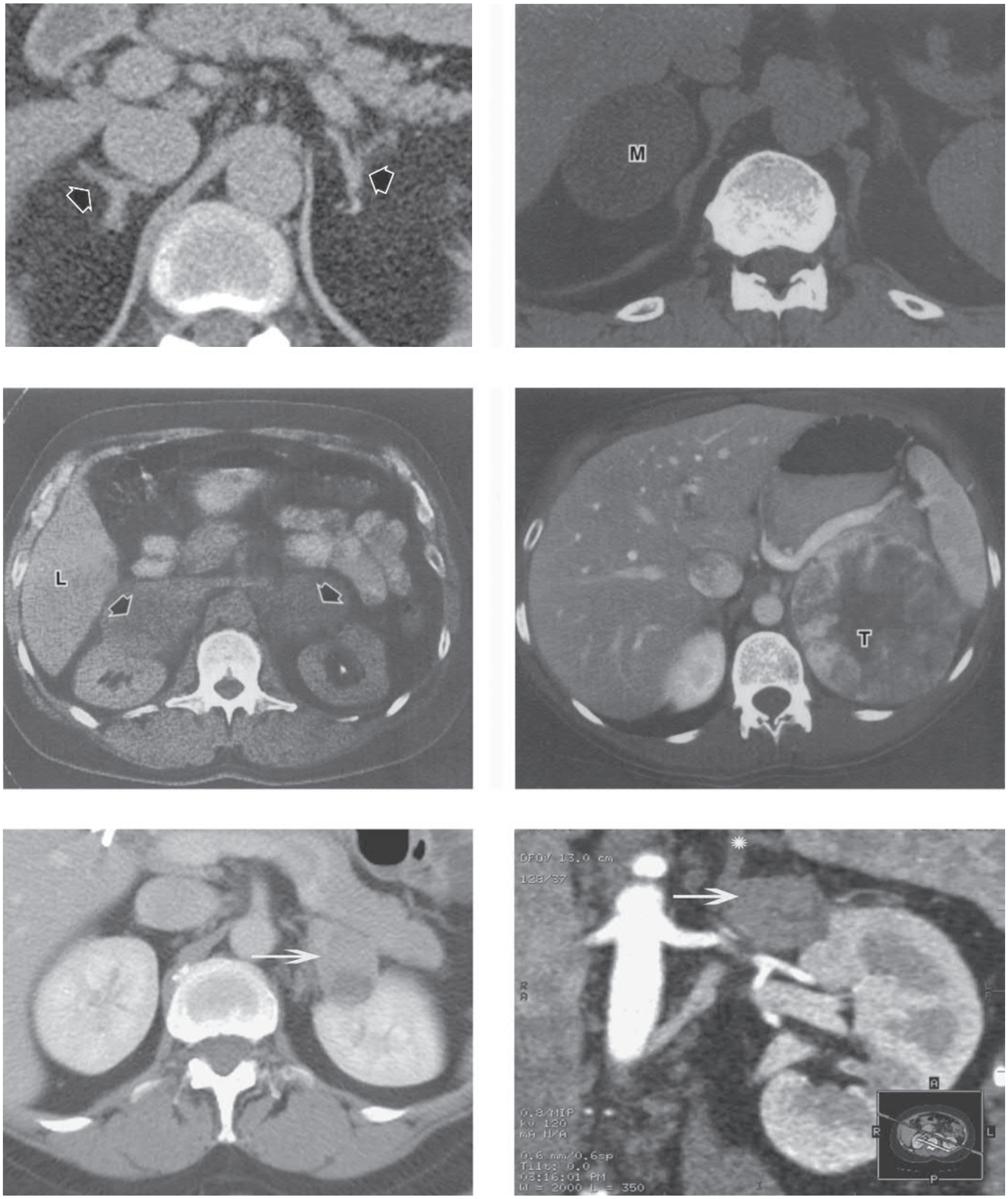
▲ **Figure 6–26.** Grayscale and Doppler sonography: acute rejection in a renal transplant. ***Upper left:*** Grayscale ultrasound image of transplant kidney shows poor corticomedullary differentiation. A small fluid collection is seen within the renal pelvis (*arrow*). Native external iliac vessels are shown as tubular hypoechoic structures (*arrowheads*). ***Upper right and lower left:*** Color Doppler images demonstrate flow within the native external iliac artery (*arrowheads*), the transplant renal artery (*long arrow*), and the interlobar arteries (*short arrow*). ***Lower right:*** Spectral Doppler analysis reveals an elevated resistive index of 0.84. These findings are compatible with, but not specific for, acute rejection. In the nonacute setting, cyclosporin toxicity or chronic rejection may also show elevated arterial resistive indices.

cross-sectional images, and relative operator independence. Carefully tailored examinations are essential. Reformatted helical image data in different planes and in three dimensions have made renal CT imaging, with renal angiography and urography, valuable in preoperative planning, such as for partial nephrectomy. Limitations of CT include restriction to the transaxial plane for direct imaging, tissue nonspecificity, low soft-tissue contrast resolution, and the need for contrast media (both oral and intravenous). Even with careful use of contrast media, tissue contrast is sometimes unsatisfactory. Finally, radiation exposure is a consideration with multisequence CT imaging (Hricak et al, 2011). Ongoing studies evaluating reduced exposure, and modifying protocols, are under way.

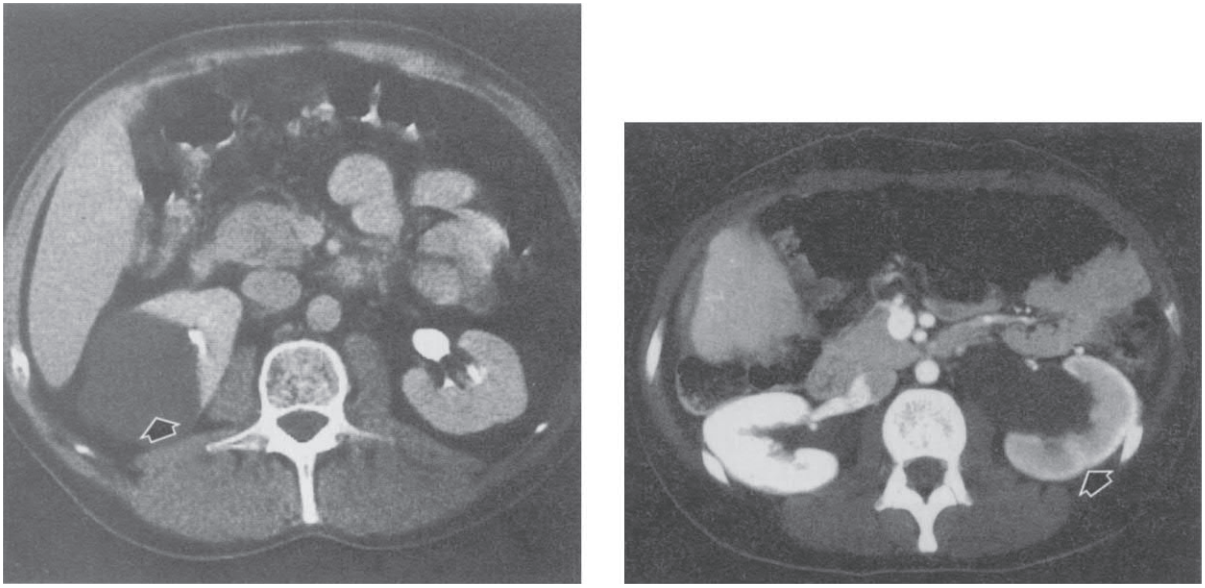
MAGNETIC RESONANCE IMAGING (FIGURES 6–34 TO 6–41)

Basic Principles

Clinical MRI is based on the nuclear properties of the hydrogen atoms in the body. Hydrogen nuclei, when considered as aggregates, and sometimes referred to as “protons,” behave



▲ **Figure 6–27.** CT scans: adrenal glands. ***Upper left:*** Normal adrenal glands (*arrows*) have inverted arrowhead or Y shape. ***Upper right:*** CT densitometry. Thin-section CT of incidental right adrenal mass (M) performed without intravenous contrast. Region-of-interest density measurement was <10 Hounsfield units (near zero), compatible with adrenal adenoma, confirmed by pathology. ***Middle left:*** Bilateral adrenal lymphoma. Enlarged adrenal glands (*arrows*) anterior to normal kidneys (L = liver). A 53-year-old man with abdominal pain and histiocytic lymphoma of the central nervous system. ***Middle right:*** Left adrenal carcinoma. Large tumor (T) in left upper retroperitoneum with necrotic or cystic changes. Differential for CT included exophytic renal carcinoma. A 52-year-old woman with pulmonary nodules (metastases). ***Lower left:*** Axial CT image reveals a predominant solid mass (*arrow*) abutting the left kidney, with areas of cystic change. ***Lower right:*** Coronal oblique reformatted image from the same patient shows the mass (*arrow*) to be inseparable from the inferior left adrenal limb (*asterisk*). Pathologically proven adrenal carcinoma.



▲ **Figure 6–28.** CT scans: kidneys. ***Left:*** Simple renal cyst. Cyst (*arrow*) has a CT number close to that of water. A 49-year-old man with flank pain. ***Right:*** New hydronephrosis, severe on left and mild on right. Dilated left renal pelvis and delayed left nephrogram (*arrow*). A 40-year-old woman with ovarian carcinoma and peritoneal metastases.

like tiny magnets, with net polarity (positive in one direction, negative in the opposite direction) oriented along an axis at any given point in space. Ordinarily, the axes of the hydrogen nuclei in the body are randomly oriented. However, if the nuclei are placed in a strong magnetic field (like that produced in an MRI scanner), they precess and wobble like a spinning top around the lines of magnetic force.

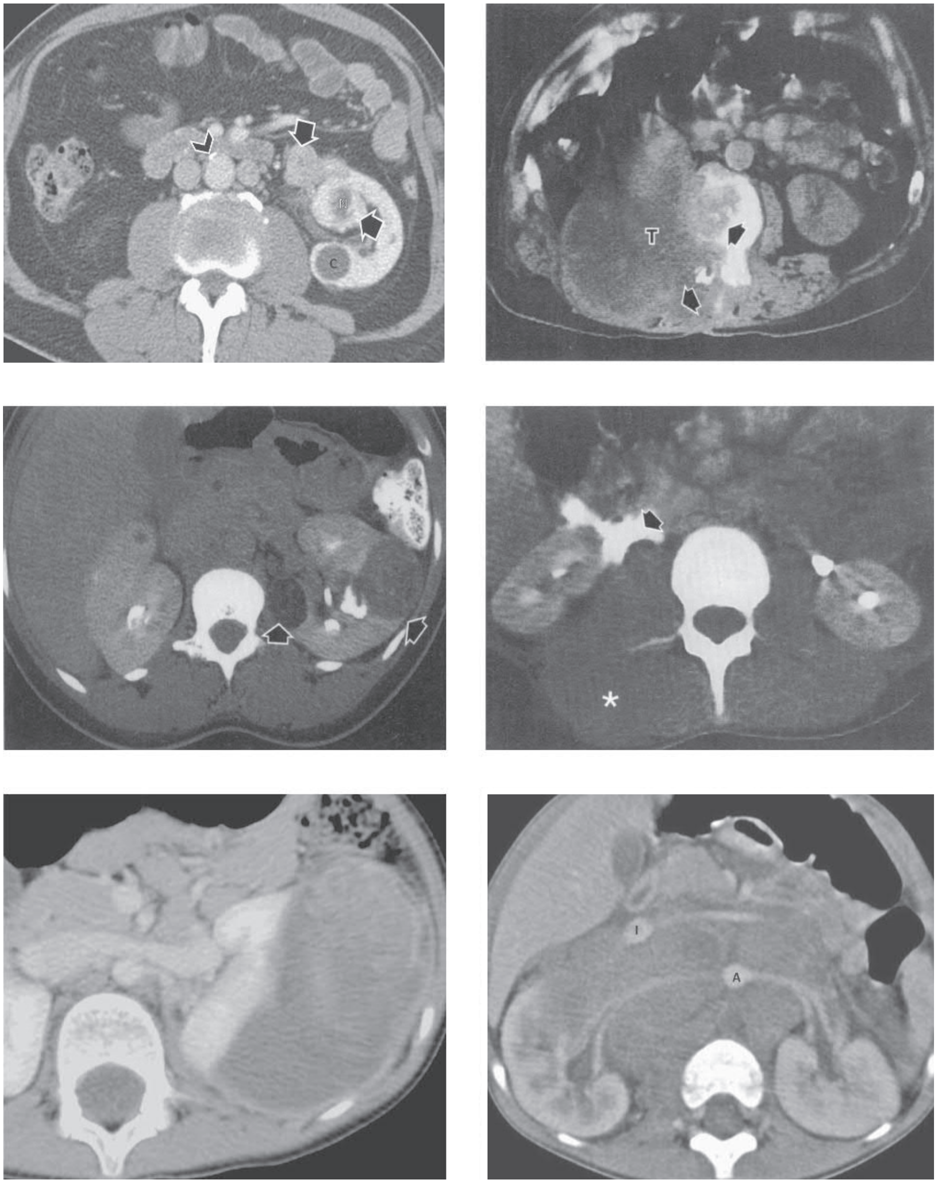
When hydrogen nuclei in a strong magnetic field are additionally stimulated by short, pulsed radio waves of appropriate frequency, they absorb energy and invert their orientation with respect to the magnetic field. At the termination of radiofrequency pulses, the hydrogen nuclei return at various rates to their original orientation within the magnetic field, emitting energy in the form of radio waves. This phenomenon is called **nuclear magnetic resonance (NMR)**. The emitted weak radio signals from the resonating hydrogen nuclei are received by sophisticated antenna, or coils, and are transformed by various computer programs into cross-sectional images.

Different MR signal intensities reflect different hydrogen densities in body tissues, as well as differing physical, cellular, and chemical microenvironments and flow (fluid) characteristics as well. The signals emitted from nuclei contain no innate spatial information. Spatial localization is achieved through varying magnetic field gradients and timing. There are biologically important nuclei other than hydrogen that are sensitive to magnetic resonance, including those of phosphorus, sodium, and potassium, but the physiologic concentrations in which these occur are lower than that of hydrogen. Imaging of these nuclei for tissue typing and mapping and as biologic tracers (MR spectroscopy) is undergoing intense research and development.

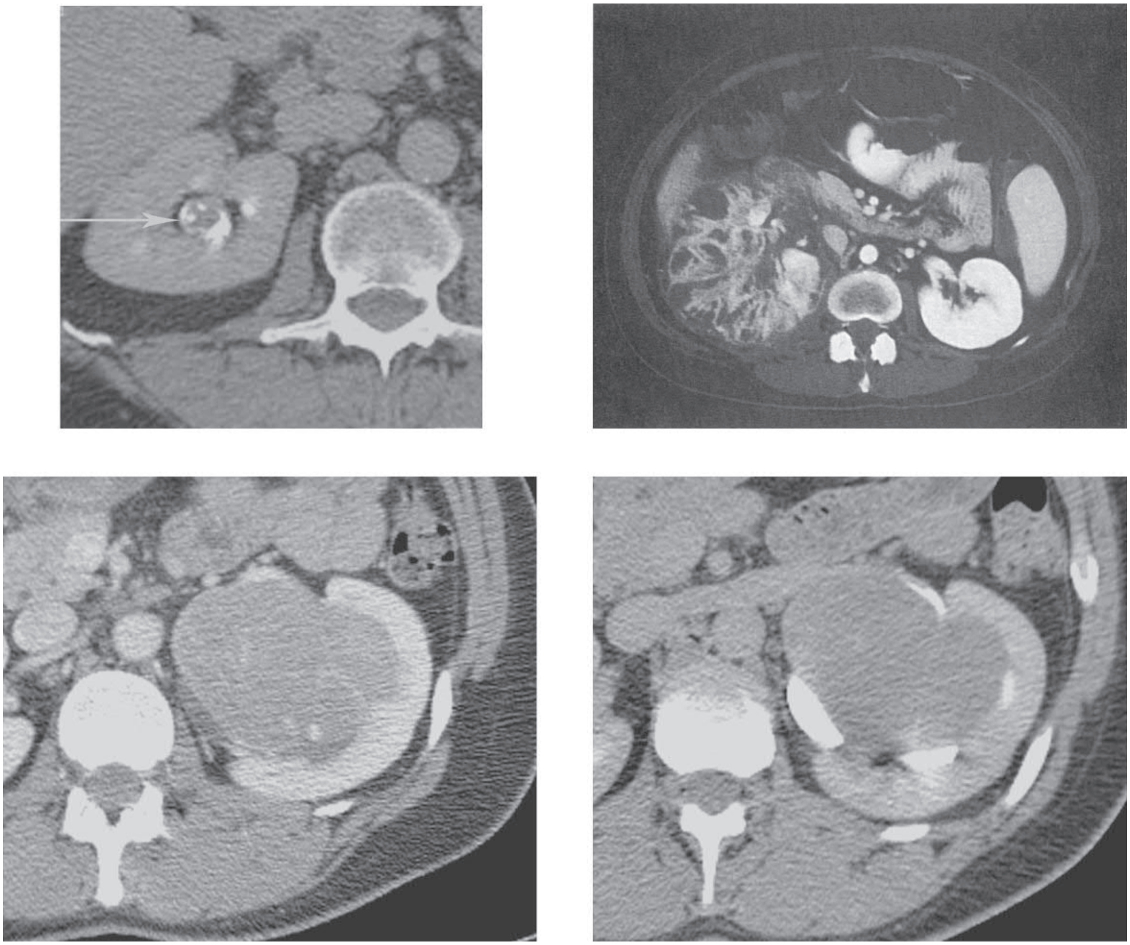
Clinical Applications

Applications for MR in renal imaging include demonstration of congenital anomalies, diagnosis of renal vein thrombosis, and diagnosis and staging of renal cell carcinoma. MR angiography is useful in evaluating renal transplant vessels, renal vein tumors or thrombosis, and renal artery stenosis.

The use of contrast media in MRI of the kidney has broadened clinical applications. Using bolus injection of gadolinium and rapid-sequence imaging, both anatomy and function of the kidney can be assessed. Gadolinium, similarly to iodine contrast media, is an extracellular contrast agent primarily excreted by glomerular filtration. Compared to iodinated contrast media, gadolinium has superior renal tolerance in patients with preexisting renal failure. Iodinated contrast agents used in radiography and CT increase attenuation linearly with their concentration. The effect of gadolinium on MR tissue signal intensity is more complex; however, in general, gadolinium causes an increase in signal intensity at lower concentrations. Cases of nephrogenic system fibrosis (NSF)



▲ **Figure 6–29.** CT scans: kidneys. ***Upper left:*** Renal cell carcinoma. The left renal tumor (*arrows*) shows heterogeneous enhancement and central necrosis (N). Note additional parenchymal cyst (C) and small calcification in the arteriosclerotic abdominal aorta (*arrowhead*). A 63-year-old man with previous right nephrectomy for renal cell carcinoma. ***Upper right:*** Recurrent renal adenocarcinoma. Massive recurrence in right renal fossa (T), with extensive invasion of posterior soft tissues and destruction of vertebral bodies (*arrows*). A 51-year-old man after right nephrectomy for carcinoma. ***Middle left:*** Renal angiomyolipomas. Bilateral heterogeneous renal masses. The larger lesions all showed areas of macroscopic fat density (*arrows*). A 35-year-old woman with probable lymphangioleiomyomatosis. ***Middle right:*** Right renal pelvic laceration. Enhanced CT scan through the kidneys showing extravasation of radiopaque material (*arrow*). Hemorrhage into the psoas and back muscles has enlarged their image (*asterisk*). A 22-year-old man with laceration of the right renal pelvis due to a stab wound. ***Lower left:*** Large palpable heterogeneous left renal mass, with confirmed hemorrhage with subcapsular extension. Wilm's tumor in a 9-year-old girl with acute-onset fever and abdominal pain. ***Lower right:*** Axial postcontrast CT of a large retroperitoneal neuroblastoma, encasing vessels, including the abdominal aorta (A) and the inferior vena cava (I).



▲ **Figure 6–30.** CT scans: kidneys. ***Upper left:*** Transitional cell carcinoma. Delayed image CT urogram demonstrates an irregular nodular filling defect in the right upper collecting system (*arrow*). ***Upper right:*** 42-year-old woman with severe right pyelonephritis. An image through the midpole of the right kidney reveals an enlarged kidney with marked destruction and striation of the renal parenchyma. Note the multiple low-density fluid collections. ***Lower left:*** Exophytic renal cell carcinoma. An image through the midpole of the left kidney shows a mass that may be of renal cortical or collecting system origin. ***Lower right:*** A lower image in the same patient reveals that the mass arises from the kidney, as the contrast-containing collecting system is splayed by the mass. The renal vein is displaced anteriorly by the mass but was free of thrombus.

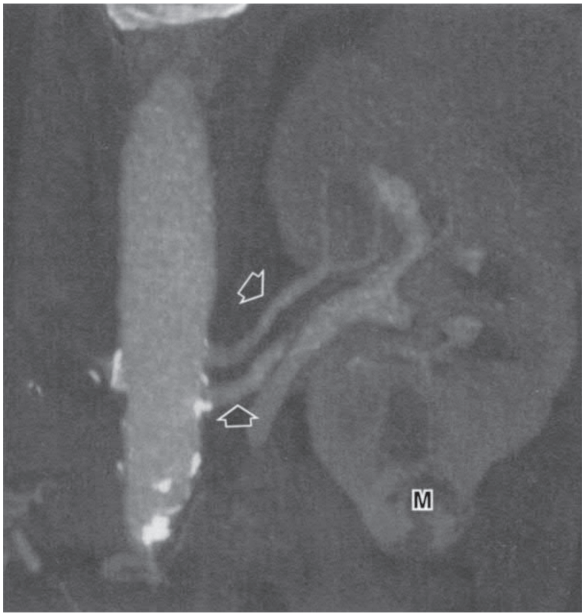
have been reported in patients with renal failure who have received gadolinium. Recent studies have suggested that patients on dialysis or with estimated glomerular filtration rates of ≤30 mL/min are at higher risk for developing NSF after gadolinium administration (Wertman et al, 2008), with cyclic chelates entailing the lowest risk for NSF (ESUR Guidelines on Contrast Media 9.0). Recent studies also discuss gadolinium deposition in the brain after repeated use (McDonald et al, 2015).

The use of gadolinium has extended the application of MRI to the evaluation of renal obstruction (MRU may be used when other studies are inconclusive) and the detection and characterization of renal tumors. Although MRI is capable of imaging blood vessels without contrast media, gadolinium bolus followed by rapid-sequence imaging is less susceptible to flow direction and overestimation of stenosis, which can be seen in noncontrast MRA imaging. Gadolinium-enhanced MRA is useful for assessing renal artery stenosis and for evaluating potential renal donors (Figure 6–39).

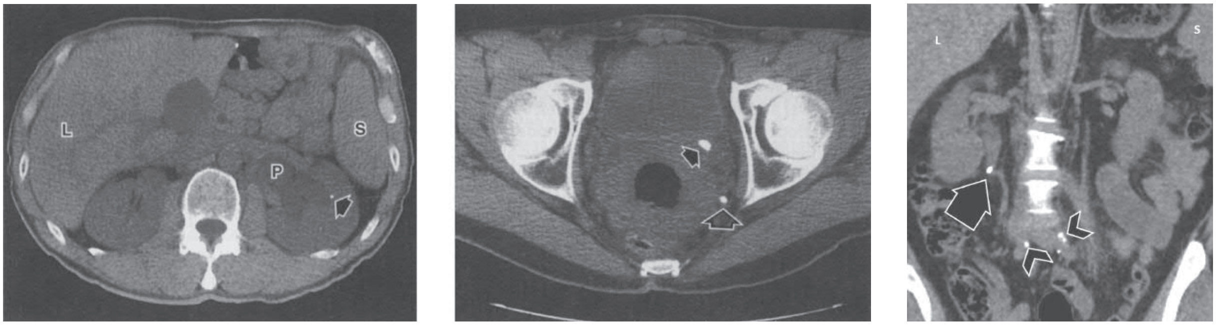
Magnetic resonance imaging is used primarily to stage bladder tumors and to differentiate between benign bladder wall hypertrophy and infiltrating malignant neoplasms. There may be a potential advantage for combined endorectal and surface coil MR staging for bladder carcinoma as well. In imaging the prostate gland, MRI is principally used to stage patients with prostate cancer (De Rooij et al, 2016; Claus et al, 2004; Coakley et al, 2002; Mazaheri et al, 2008). The addition of functional MRI sequences (eg, dynamic contrast-enhanced MRI, diffusion-weighted MRI, and MR spectroscopy) to morphological MRI may improve diagnostic performance and reduce interobserver variability in this setting (Shukla-Dave et al, 2007; Barentsz et al, 2012; Fusco et al, 2016). MRI of the testis is appropriate when other imaging studies are inconclusive and is applicable to the evaluation of trauma, epididymo-orchitis, tumors, and undescended testes in specific scenarios. MRI of the penis can be of help when penile fracture is suspected (Uder et al, 2002).

A modification of the MRI technique, called **chemical shift imaging**, can detect microscopic amounts of fat within lesions (Figure 6–35, middle images). This technique is commonly used to characterize adrenal masses. Adrenal masses containing fat are either adrenal adenomas or myelolipomas, so the CT or MRI demonstration of fat in an adrenal lesion characterizes it as a benign lesion, even in the oncologic patient.

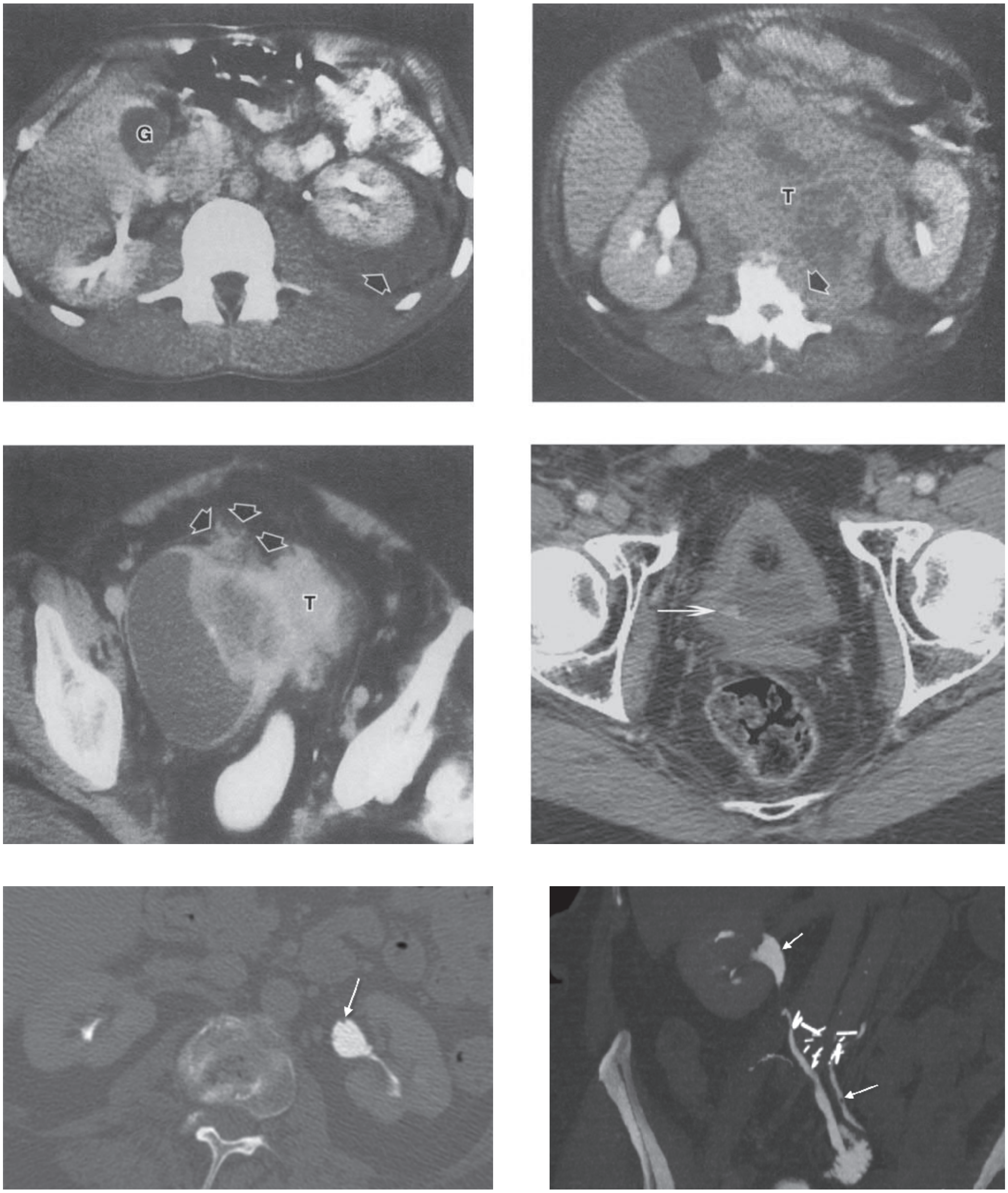
Magnetic resonance urography utilizes the sensitivity of MR imaging to demonstrate fluid (urine), producing urogram-like pictures without the need for contrast media. This technique is sensitive in the detection of ureterohydronephrosis



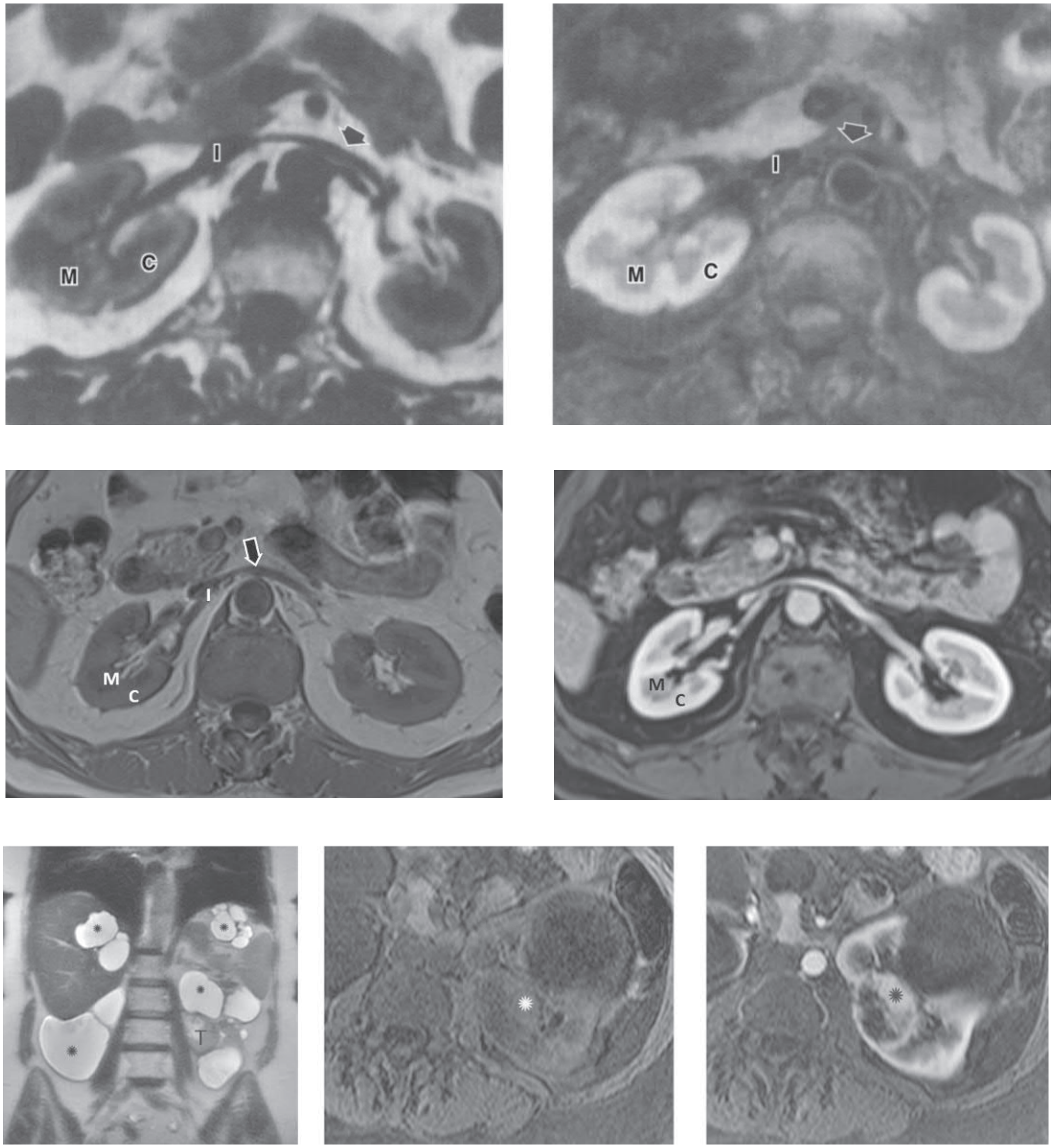
▲ **Figure 6–31.** Three-dimensional computed tomography (CT) and CT angiography (CTA) for renal mass, performed on multidetector CT scanner. Coronal oblique reformatted image with volume rendering shows a small enhancing mass (M) in the lower pole of the left kidney. The kidney has two renal arteries (*arrows*). The lower one, which serves the tumor, is the primary artery. A 69-year-old man with solitary kidney and indeterminate lesion on prior CT.



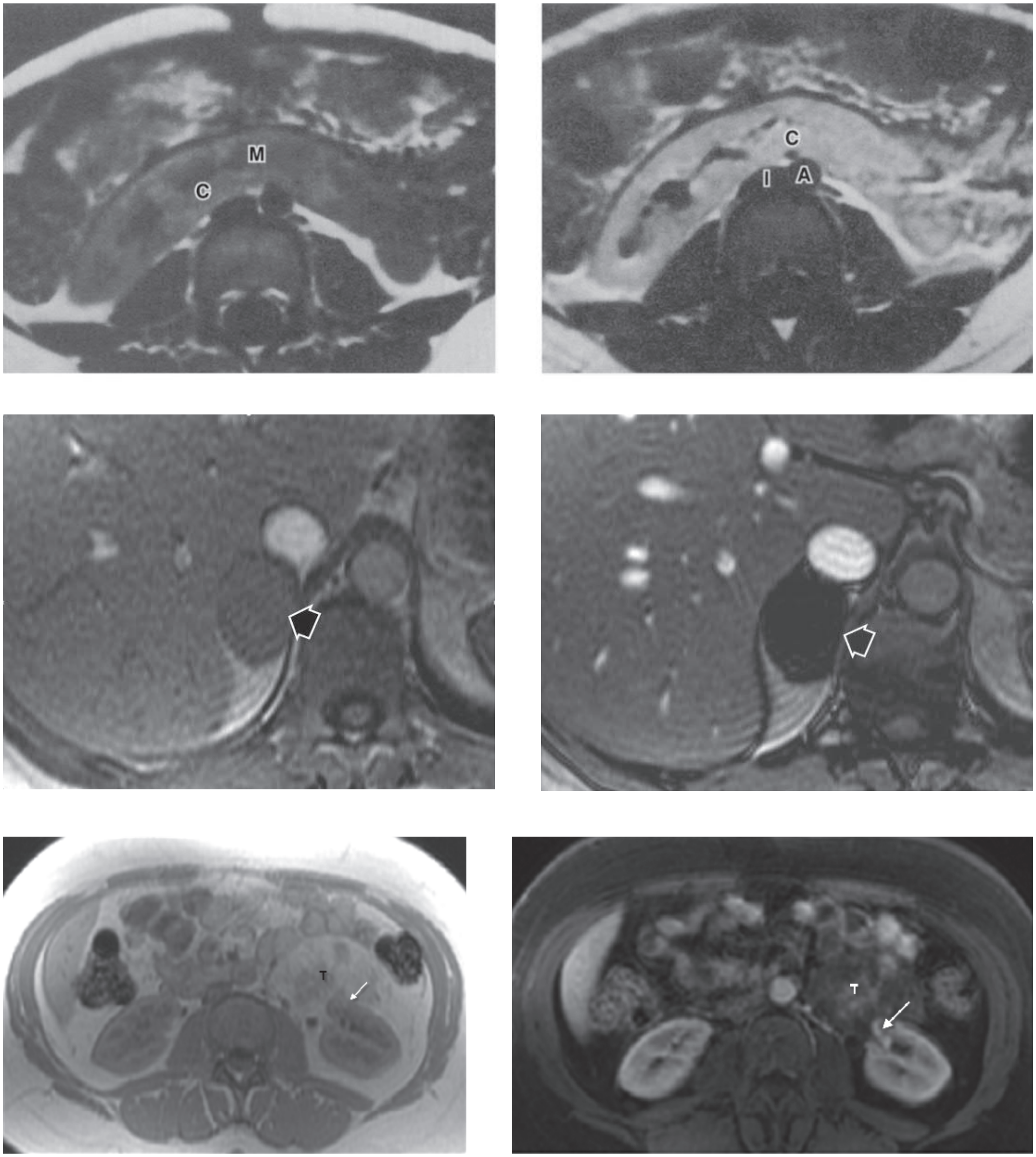
▲ **Figure 6–32.** Helical computed tomography (CT) without oral or intravenous contrast in a 42-year-old man with left flank pain. ***Left:*** CT image through the kidneys shows enlargement of the left kidney compared with the right, left pelvocaliectasis (P), and a stone in the midpole of the left kidney (*arrow*). (L = liver, S = spleen.) ***Middle:*** CT image through the base of the bladder shows an 8-mm stone (*arrow*) at the left ureterovesical junction with associated edema involving the left hemitrigone. Posterior to the ureteral stone is a 5-mm phlebolith (*open arrow*) within a pelvic vein. ***Right:*** Coronal nonenhanced CT shows a stone in the right ureter (*arrow*) with associated pelviectasis. Note arteriosclerosis in the iliac arteries (*arrowheads*). (L=liver, S=spleen.)



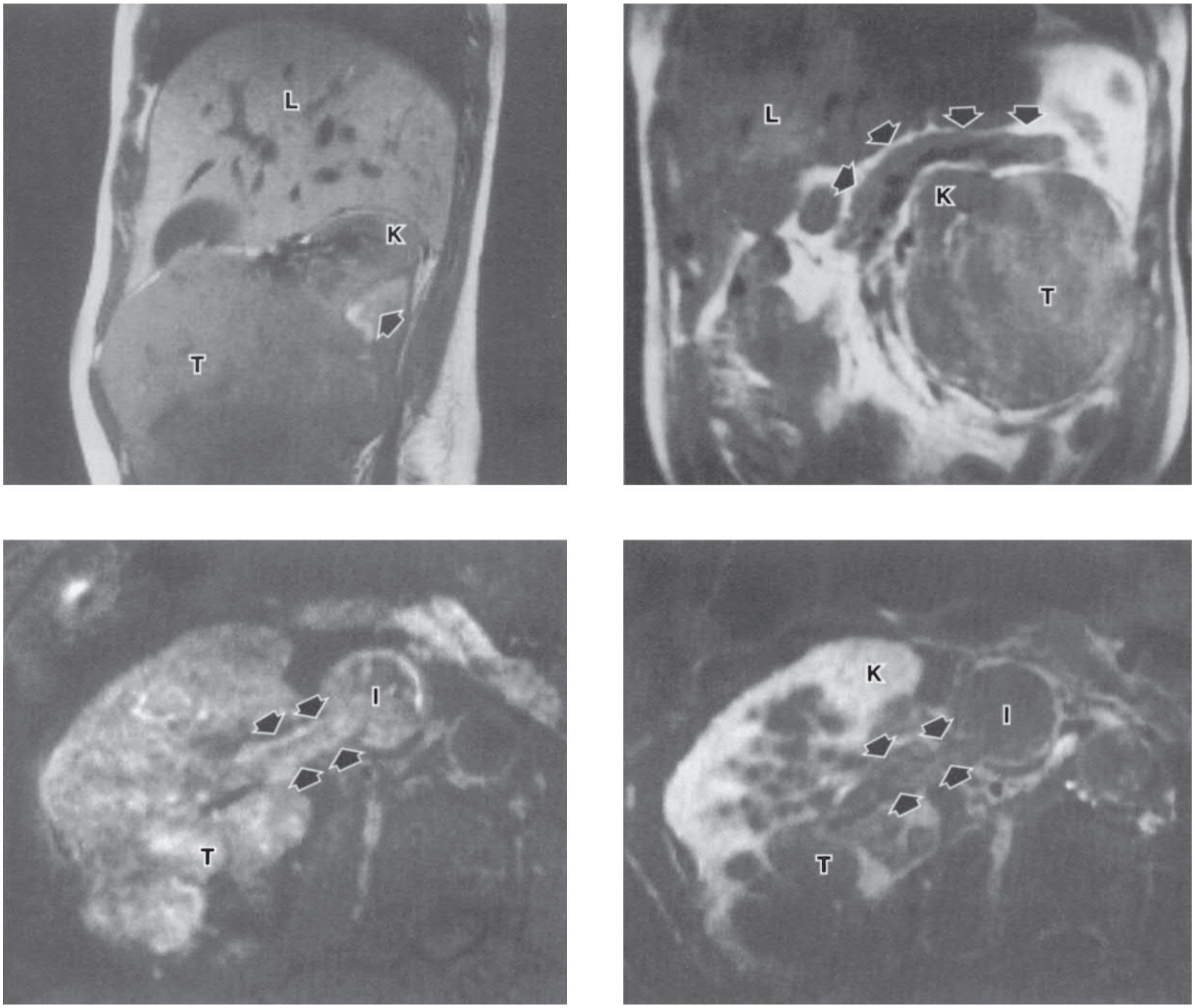
▲ **Figure 6–33.** CT scans: retroperitoneum, bladder, prostate. ***Upper left:*** Perirenal hematoma. Hematoma (*arrow*) displaces the left kidney anteriorly (G = gallbladder). A 16-year-old boy with acute glomerulonephritis; low-grade fever and left flank pain following left renal biopsy. ***Upper right:*** Retroperitoneal metastatic seminoma. Large retroperitoneal mass of metastatic nodes (T) destroying vertebral body (*arrow*), obliterating outlines of central abdominal and retroperitoneal structures, and displacing kidneys laterally and bowel anteriorly. A 46-year-old man with metastatic anaplastic testicular seminoma. ***Middle left:*** CT scan, transitional cell carcinoma of the urinary bladder with tumor (T) extension into the bladder diverticulum. There is tumor extension into the perivesical fat (*arrows*). ***Middle right:*** CT urogram in arterial phase, enhancing 5-mm transitional cell carcinoma of the urinary bladder (*arrow*). ***Lower left:*** Ureteritis cystica on CT urogram. Punctate rounded filling defect (*arrow*) in left renal pelvis on 12-minute delayed excretion images after intravenous contrast administration. ***Lower right:*** Coronal delayed reformat demonstrates other similar punctate collecting system filling defects. A 77-year-old woman after cystectomy on surveillance with stable, multiple punctate rounded filling defects bilaterally and negative urine cytology.



▲ **Figure 6–34.** Magnetic resonance imaging (MRI) appearance of the normal kidney. ***Upper left:*** T1-weighted conventional spin-echo image showing detailed anatomy of the kidney with differentiation between higher-signal-intensity cortex (C) and lower-signal-intensity medulla (M). Left renal vein (*arrow*), inferior vena cava (I). ***Upper right:*** T1-weighted spin-echo image using fat saturation technique. Because the fat signal has been suppressed, the computer automatically adjusts the gray scale of the signal intensity, rendering even better contrast between higher-signal-intensity cortex (C) and lower-signal-intensity medulla (M). ***Middle left:*** T1-weighted gradient echo image showing detailed anatomy of the kidneys with differentiation between higher-signal-intensity cortex (C) and lower-signal-intensity medulla (M). Left renal vein (*arrow*), inferior vena cava (I). ***Middle right:*** T1-weighted fat-saturated image after contrast injection. There is excellent contrast between higher-signal-intensity cortex (C) and lower-signal-intensity medulla (M). ***Lower left:*** Coronal T2-weighted image shows multiple renal and hepatic cysts (*asterisk*), as well as a partially solid and cystic left renal mass (T) in this adult female with polycystic kidney disease. ***Lower middle:*** Noncontrast T1-weighted fat saturation volume acquisition scan, used for dynamic imaging. The left renal mass is subtle on this precontrast scan (*asterisk*). ***Lower right:*** Arterial phase scan obtained following gadolinium-DTPA injection of contrast medium. The left renal mass (*asterisk*) shows avid enhancement of solid components. The addition of gadolinium adds significant soft-tissue contrast.



▲ **Figure 6–35.** Magnetic resonance (MR) images. ***Upper images:*** Horseshoe kidney. Nonenhanced T1-weighted image (***upper left***) (m = medulla; c = renal cortex). Gadolinium-DTPA-enhanced T1-weighted image (***upper right***). Following injection of the contrast medium, there is uniform enhancement of the renal cortex (C). The addition of the contrast enhancement shows that the part of the kidney in front of the aorta (A) and the inferior vena cava (I) is functioning renal parenchyma. ***Middle images:*** Chemical shift imaging, adrenal adenoma. On in-phase gradient T1-weighted image (***middle left***), there is a soft-tissue-intensity 3-cm mass in the right adrenal gland (*arrow*). Opposed phase T1-weighted image (***middle right***) shows marked signal loss in the lesion consistent with intracellular lipid and, therefore, a benign adenoma. A 40-year-old woman with indeterminate adrenal lesion noted on prior computed tomography (CT). ***Lower left:*** Biopsy-proven angiomyolipoma. Axial T1-weighted gradient echo in-phase imaging reveals a mass (T) arising off anterior interpolar left kidney. Renal contour defect (*arrow*) noted where mass originates. ***Lower right:*** Postintravenous gadolinium fat saturation T1-weighted image reveals a large amount of low-signal-intensity fat within the mass as well as vascular supply (*arrow*) arising via vessels extending from a defect in the renal cortex.



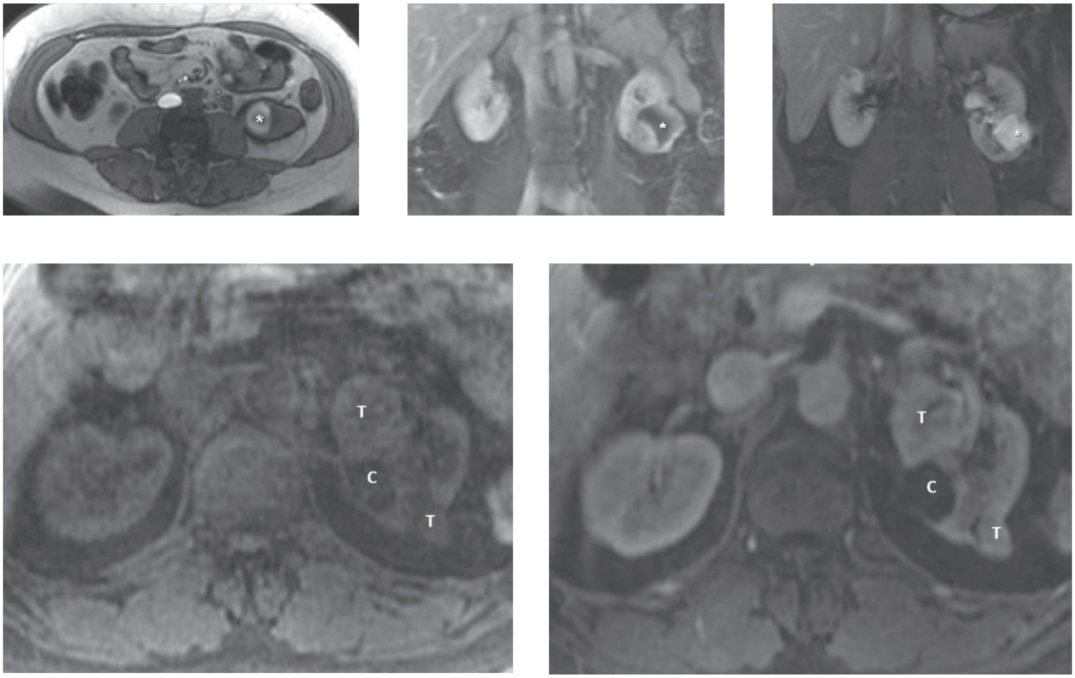
▲ **Figure 6–36.** Magnetic resonance imaging (MRI) appearance of renal cell carcinoma. The advantages of MRI are multiplanar imaging and the use of contrast media for better tumor characterization. ***Upper left:*** Sagittal T1-weighted image demonstrating a large renal cell carcinoma (T) arising from the inferior pole of the right kidney (K). Tumor extension in the posterior perirenal space (*arrow*). Liver (L). ***Upper right:*** Coronal image of a large renal cell carcinoma (T) replacing almost entire parenchyma of the left kidney (K). Superior displacement of the pancreas (*arrows*). Liver (L). ***Lower images:*** Fat saturation images before and after injection of the contrast medium. Heterogeneous tumor (***lower right***) in the posterior part of the right kidney shows heterogeneous enhancement following injection of gadolinium. The tumor is extending into the renal vein (*arrows*) and to the inferior vena cava (I).

and is particularly useful in patients in whom contrast material is contraindicated, such as patients with prior contrast reactions or renal failure. Upper tract tumor can also be demonstrated (Takahashi et al, 2008, 2009).

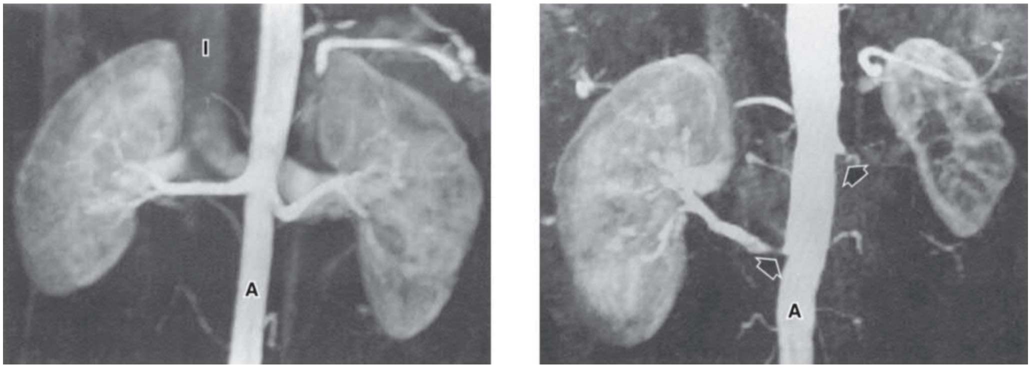
Diffusion-weighted imaging, a technique under active investigation for urologic imaging with recent clinical implementation, exploits restricted water diffusion in diseased tissue. This technique has shown added benefit and promise, particularly for lesion detection in oncologic imaging (Giannarini et al, 2012; Lim et al, 2009; Mazaheri et al, 2008; Seitz et al, 2009).

Advantages and Disadvantages

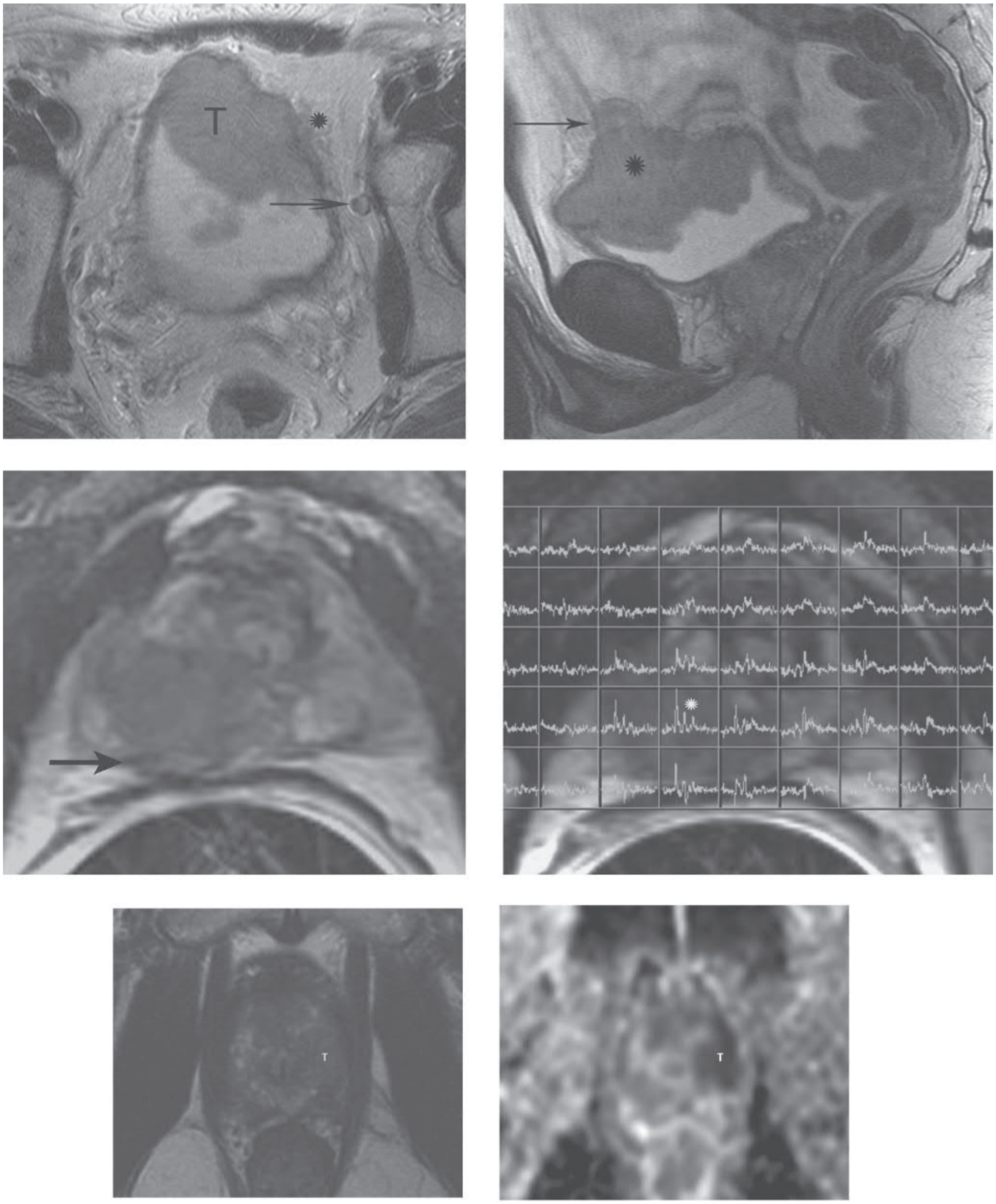
Advantages of MRI include direct imaging in any plane desired (although transverse, sagittal, and coronal are most standard), choice of large or small field of view, excellent soft-tissue contrast, imaging without exposure to ionizing radiation, and



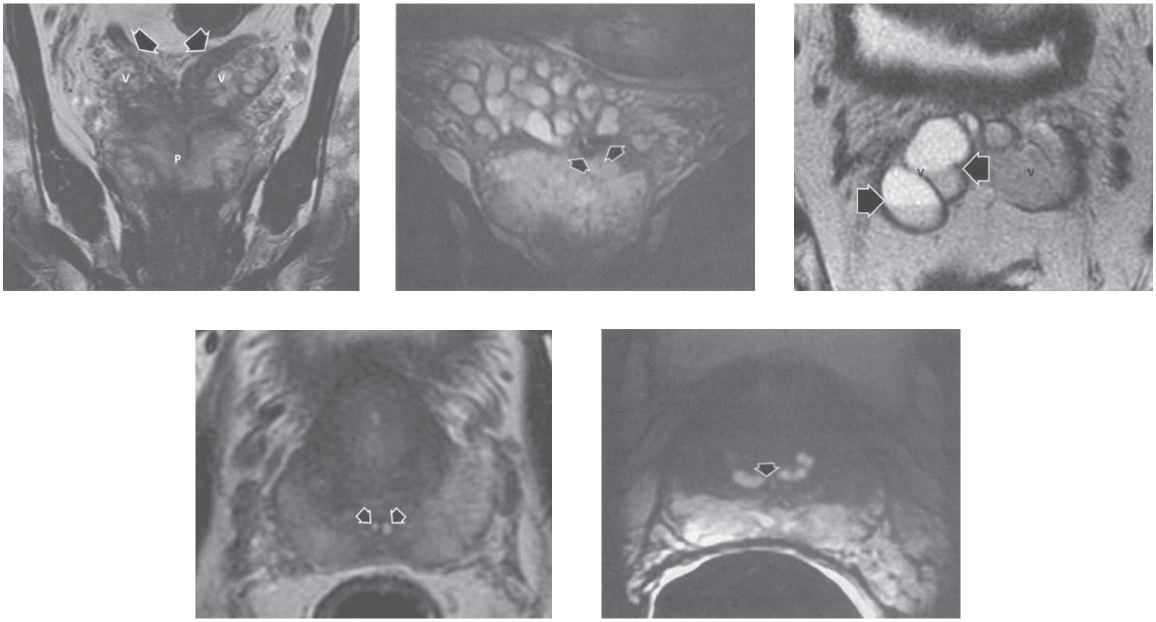
▲ **Figure 6–37.** A 42-year-old woman with abdominal pain after karate kick with gross hematuria. ***Upper left:*** Axial T1-weighted out-of-phase gradient echo image reveals high T1 signal intensity indicative of hemorrhage within a left renal lesion (*asterisk*), confirmed as cystic on other sequences. ***Upper middle:*** Coronal T1 fat saturation image after intravenous gadolinium administration shows lack of cyst enhancement (*asterisk*). ***Upper right:*** Delayed postcontrast imaging confirms communication with collecting system, showing cyst contents filling with high signal gadolinium (*asterisk*). Hemorrhage within a calyceal diverticulum after trauma. ***Lower images:*** Pre- and postcontrast and magnetic resonance imaging (MRI) of two renal cell carcinomas adjacent to a cyst in another patient. ***Lower left:*** Precontrast T1-weighted fat-saturated image shows little difference of intensities for the cyst (C), tumor (T), and normal renal parenchyma. ***Lower right:*** Postcontrast image. The cyst (C) is nonenhancing. The renal cell carcinomas (T) show heterogeneous contrast enhancement.



▲ **Figure 6–38.** Gadolinium-enhanced renal magnetic resonance angiography (MRA). ***Left:*** Maximum intensity projection (MIP) image from a renal MRA in a 22-year-old potential renal donor. The renal arteries are normal. ***Right:*** MIP image from a renal MRA in a 56-year-old man with suspected renovascular hypertension shows an atrophic left kidney with an occluded left renal artery (*arrow*) and a severely stenotic right renal artery (*open arrow*). The collateral capsular renal vessels are not seen. (A = aorta, I = inferior vena cava.)



▲ **Figure 6–39.** Magnetic resonance imaging (MRI) examination of the pelvis. The upper images are examples of the ability of MRI to evaluate bladder neoplasms. ***Upper left:*** Axial T2-weighted image. A large anterior bladder tumor (T) shows associated perivesicular fat stranding (*asterisk*), raising the suspicion for extension through the muscularis. A prominent vessel (*arrow*) in the left obturator region exited through the obturator foramen on more inferior images. ***Upper right:*** T2-weighted sagittal image. The tumor (*asterisk*) extends into the urachal remnant (*arrow*). ***Middle and lower rows:*** Prostate cancer. Axial T2-weighted image (***middle left***) shows dominant right midgland peripheral and transition zone tumor with gross posterior extracapsular extension (*arrow*). Superimposed spectroscopy confirms depleted citrate (*asterisk*) compared to the adjacent choline and creatine peaks in the region of tumor (***middle right***). ***Lower left:*** Axial T2-weighted image in another patient demonstrates a homogeneously hypointense left apex to midgland lesion (T). ***Lower right:*** Apparent diffusion coefficient mapping confirms restricted diffusion within the tumor (T). Gleason 4 + 4 biopsy-proven tumor.



▲ **Figure 6–40.** Magnetic resonance imaging (MRI) of seminal vesicles, ductus deferens, and ejaculatory ducts. ***Upper left:*** Coronal T2-weighted image, normal seminal vesicles, ductus deferens, and ejaculatory ducts. The ampullae of the ductus deferens (*arrows*) are immediately medial to the seminal vesicles (V). The seminal vesicles are draped over the prostate gland (P). ***Upper middle:*** Axial T2-weighted image through the seminal vesicles (V). Seminal vesicles are filled with high-T2-signal-intensity fluid. Thickening of the fluid causes sedimentation within the vesicles (*arrows*). ***Upper right:*** Seminal vesicle and ductus deferens calculi. Coronal T2-weighted images show low-signal calculi within the proximal ductus deferens and medial aspect of the seminal vesicle on the left side (*arrows*). The patient had a history of prostatitis, prostatic pain, and hemorrhagic ejaculate. ***Lower left:*** Axial T2-weighted image through the prostate. The peripheral zone is of normal high signal intensity. The normal ejaculatory ducts (*arrows*) are identified as two small foci ducts of high signal intensity within the lower-signal-intensity central zone. ***Lower right:*** Axial T2-weighted image through the prostate reveals a low-signal-intensity calculus (*arrow*) within the right ejaculatory duct (same patient as in ***upper right*** image).

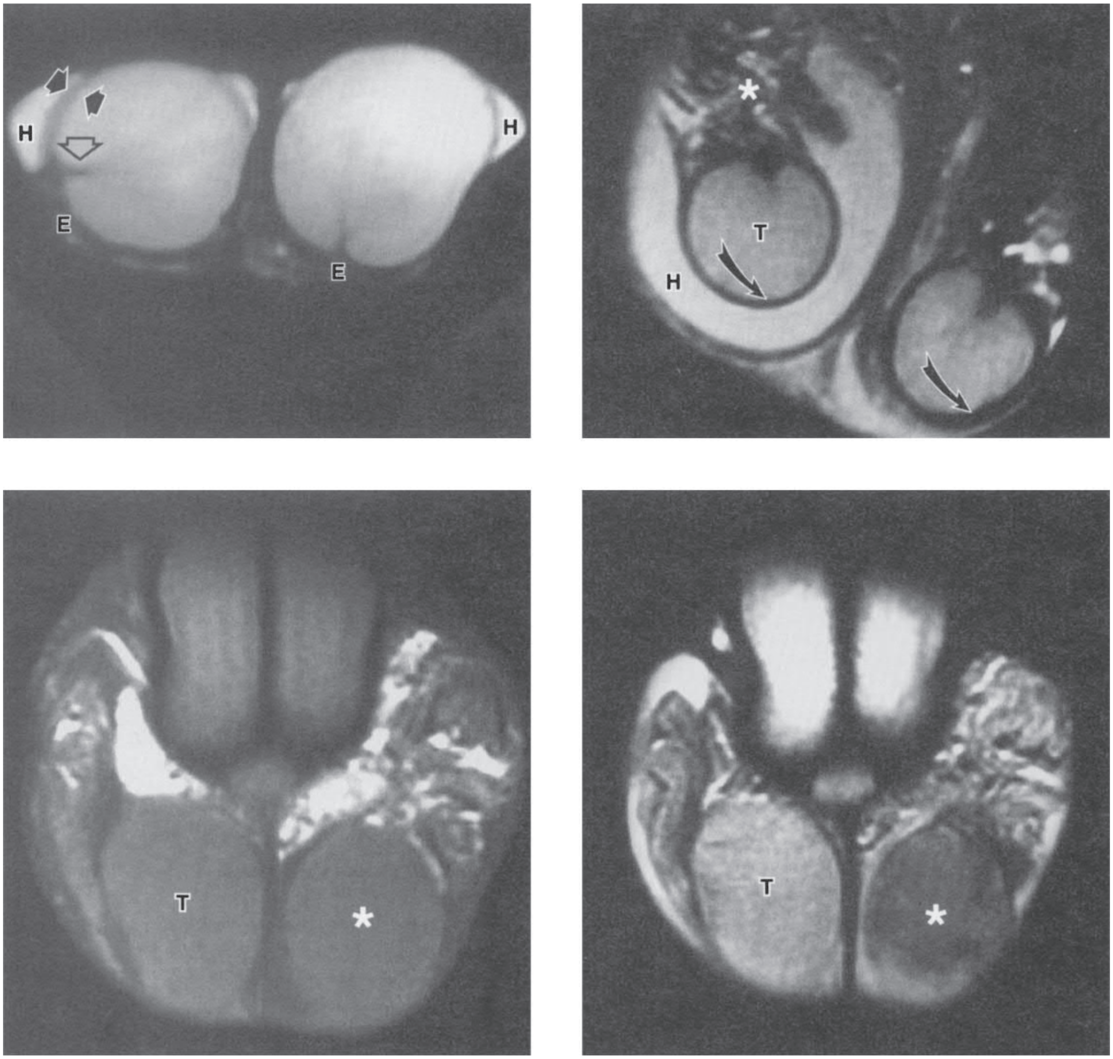
(as compared to ultrasound) less operator dependence. MRI can image blood vessels and the urinary tract without contrast material. MR scanning, however, is not without drawbacks. The scanning time is relatively slow, and as a result image clarity is often inferior compared with CT. Absolute contraindications to MRI include the presence of (1) intracranial aneurysm clips, unless the referring physician is certain that the clip consists of a nonferromagnetic material (such as titanium); (2) intraorbital metal fragments; and (3) any electrically, magnetically, or mechanically activated implants (including cardiac pacemakers, biostimulators, neurostimulators, cochlear implants, and hearing aids). Relative contraindications such as pregnancy should always be viewed in the light of risk versus benefit of the examination.

COMPARISON OF IMAGING METHODS (FIGURES 6–42 TO 6–45)

As new imaging methods have been developed, changes have occurred in patterns of use for each type of imaging. For example, increased familiarity with and confidence in sonography and CT scanning have resulted in a substantial decrease in the use of many long-established conventional uroradiologic studies such as EU (Lang et al, 2003).

Several factors are involved in these changes: (1) the increased effectiveness of newer imaging methods over older ones for some aspects of urodiagnosis; (2) the availability of equipment, trained technical personnel to operate it, and physicians to interpret the results; (3) increased awareness of the hazards of ionizing radiation (Nawfel et al, 2004); and (4) the desire to use noninvasive examinations if possible.

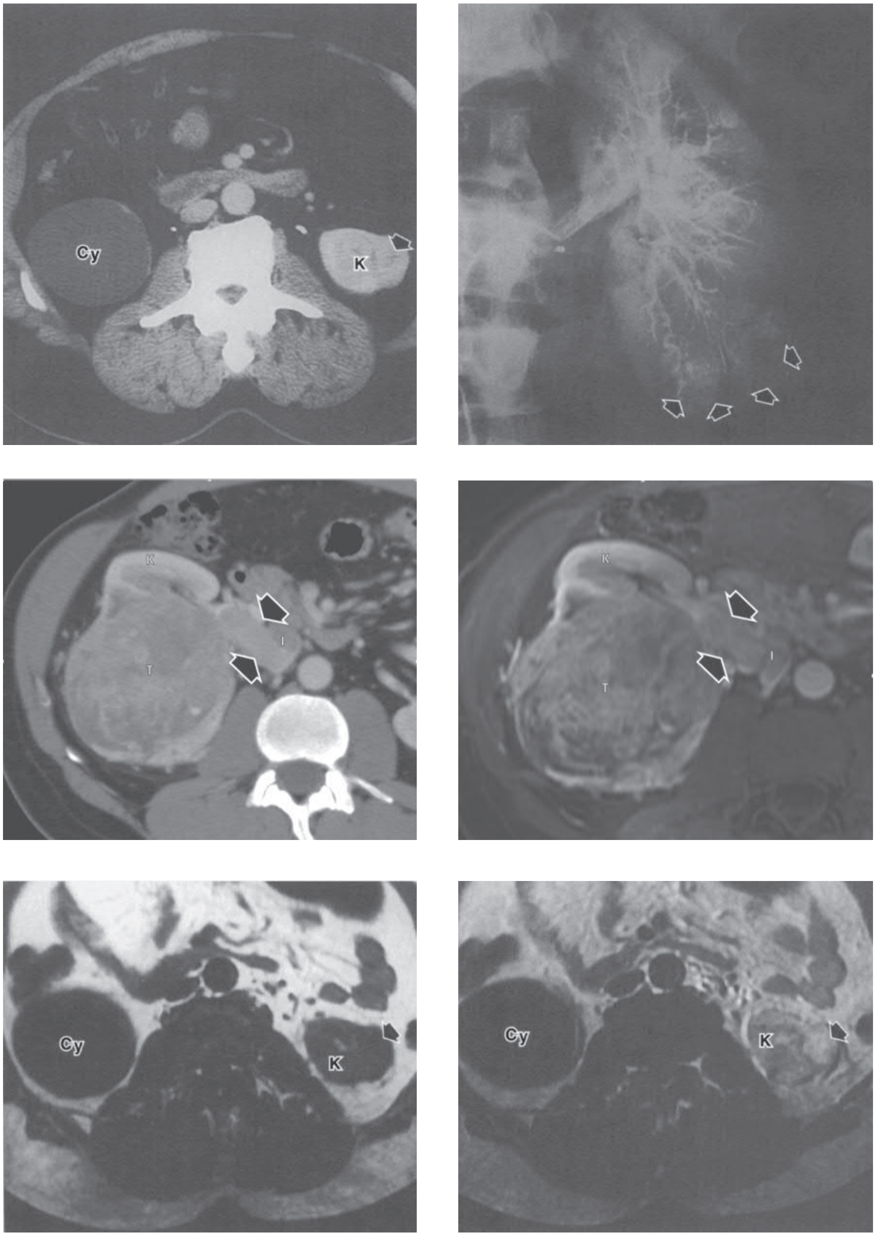
Because so many different types of imaging are available, each with different costs, risks, and areas of effectiveness, it may be difficult for the clinician to decide which method will yield the most information with the least cost and risk. One study may be critical in one diagnostic situation but useless in another. For example, sonography is an excellent noninvasive, relatively inexpensive method for differentiating simple cysts from other mass lesions in the kidney but is much less effective in imaging the adrenal glands and ureters than is CT scanning. Sonography also relies considerably on the skill of



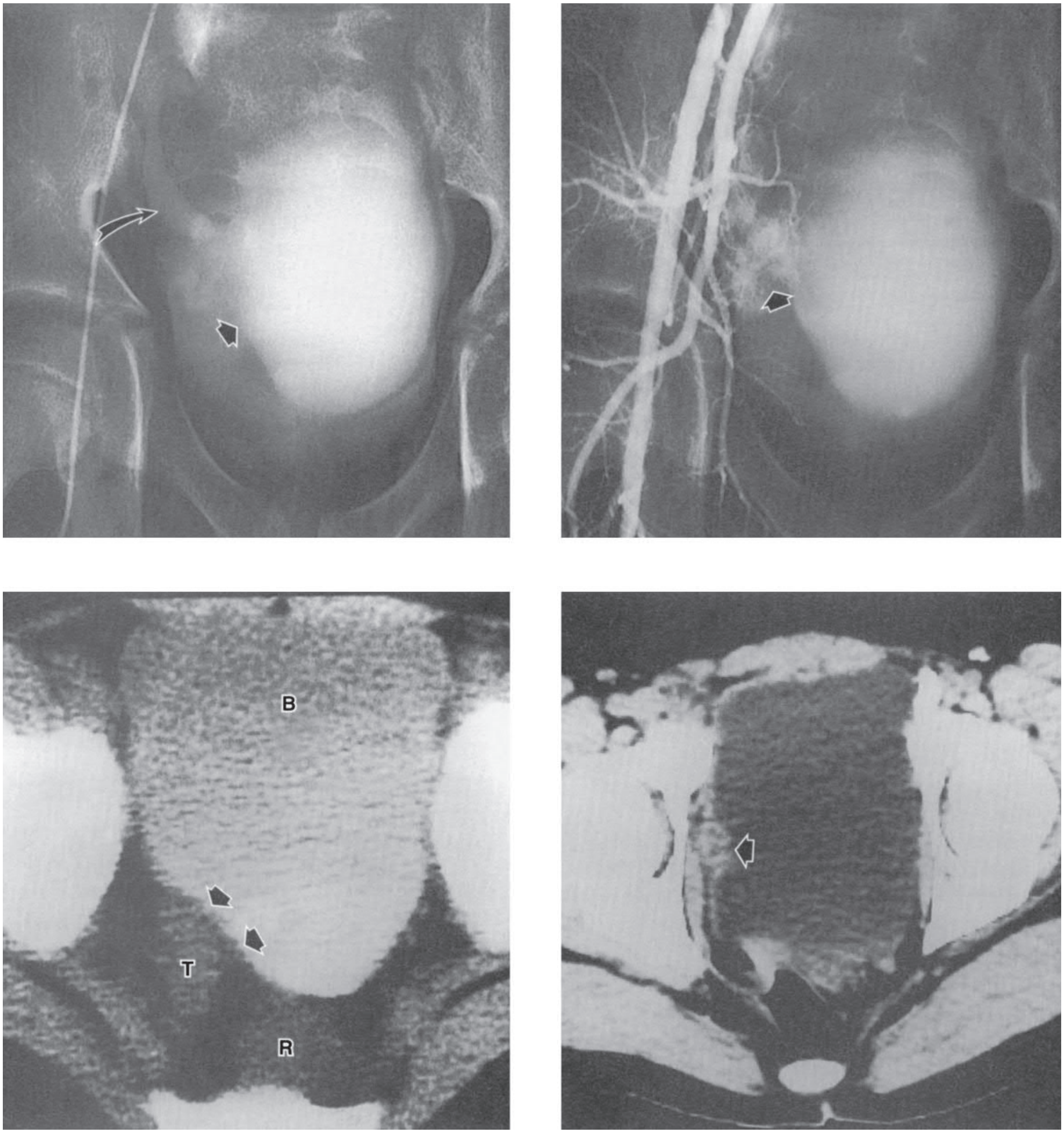
▲ **Figure 6–41.** Magnetic resonance imaging (MRI) appearance of scrotal contents. ***Upper left:*** Normal testis, T2-weighted image. The testicular tissue is of homogeneous high signal intensity. The tunica albuginea (*arrows*) demonstrates low signal intensity as does the mediastinum testis (*open arrowhead*). A small amount of fluid-hydrocele (H). Epididymis (E) is of low signal intensity. ***Upper right:*** Hydrocele of the right scrotum (T2-weighted image). Hydrocele (H) demonstrates high signal intensity. Testis (T). Tunica albuginea (*curved black arrows*). Varicocele (*asterisk*). ***Lower images:*** A testicular tumor. On the proton density image (***lower left***), the signal intensity from both testicles is similar. On the T2-weighted image (***lower right***), testicular tumor (*asterisk*) demonstrates lower signal intensity as compared with the higher signal intensity of the normal testicular tissue (T).

the operator. CT scanning produces excellent images and is currently the preferred imaging method for examination of the retroperitoneum. MRI rivals CT scanning in imaging capability for some structures, such as the kidney, but has surpassed CT in imaging the pelvis. With advances in equipment and techniques, the use of MRI in urology will likely grow.

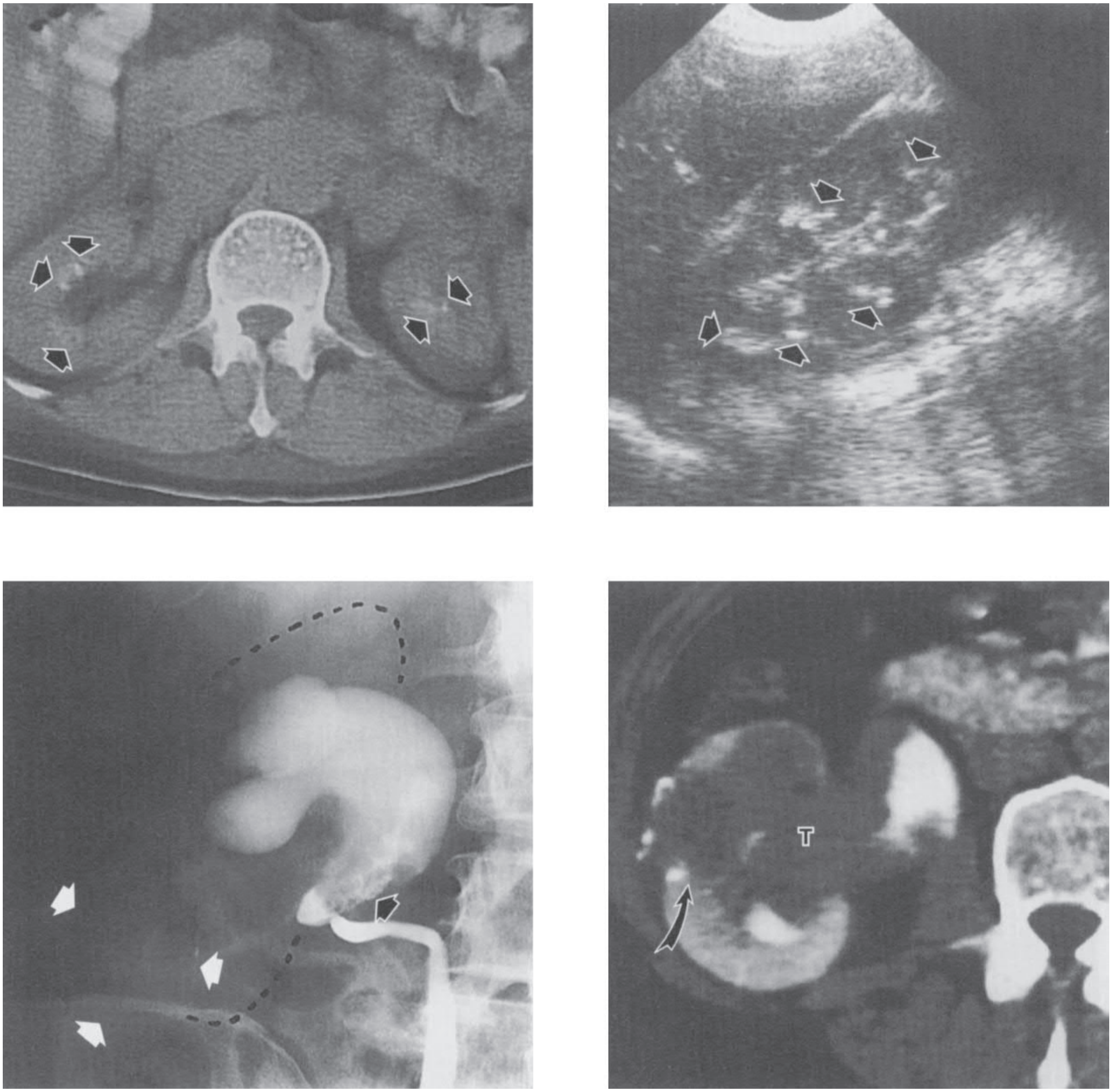
The patient and the clinician both benefit from careful consultation with the radiologist to ensure that the methods of imaging chosen are of value in diagnosis and treatment planning, and that they do not duplicate or merely confirm established findings, with loss of time and additional expense.



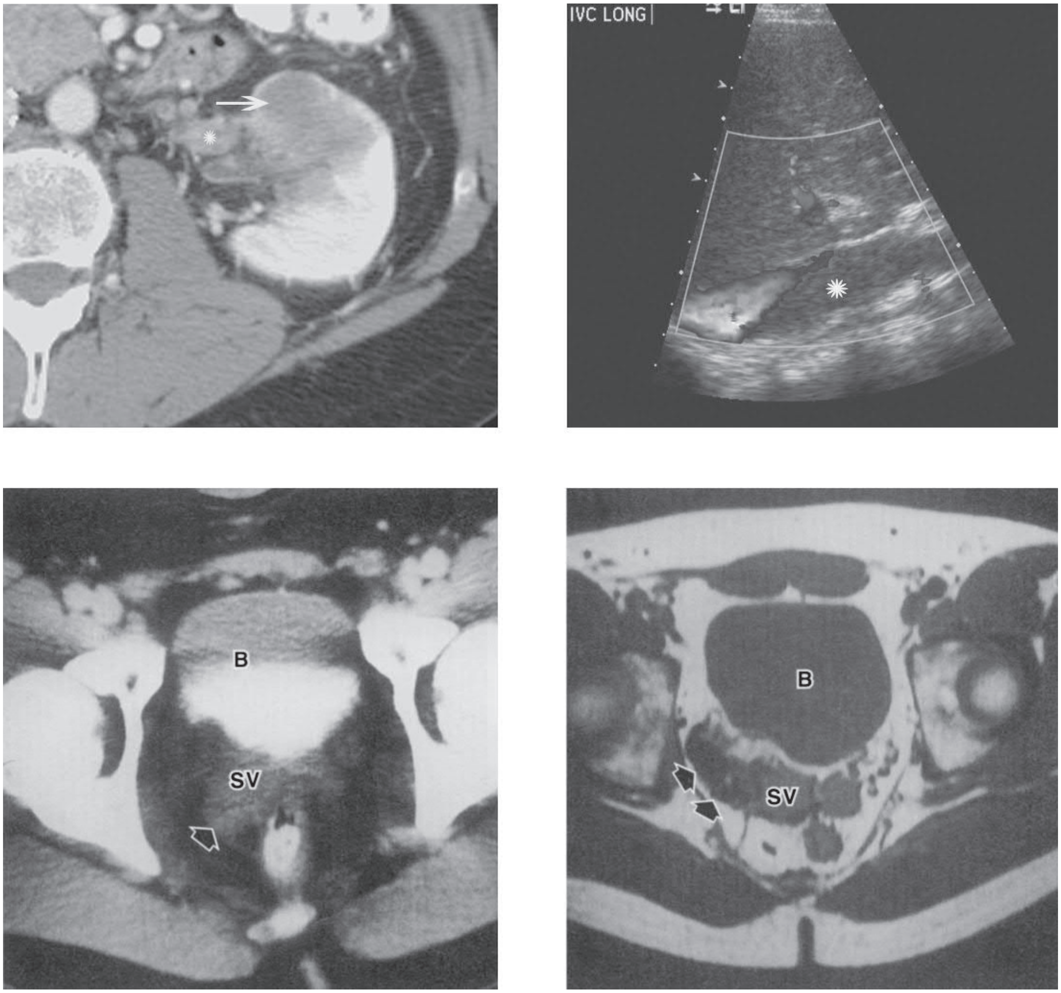
▲ **Figure 6–42.** Comparison of imaging methods in the evaluation of renal cell carcinoma. ***Upper left:*** Computed tomography (CT) scan showing a renal cyst (Cy) in the right kidney. There is bulging (*arrow*) in the contour of the left kidney (K), but it is difficult to discern if the lesion represents a neoplasm. ***Upper right:*** Angiogram showing small vascular lesions in the inferior pole of the left kidney (*arrows*). ***Middle images:*** Postcontrast CT and MRI scans showing a heterogeneously enhancing tumor (T) in the posterior part of the right kidney (K) with tumor thrombus extending into the renal vein (*arrows*) and the inferior vena cava (I). ***Middle left***: Postcontrast CT showing heterogeneous tumor. ***Middle right:*** Fat saturation MR image after injection of contrast medium. ***Lower images:*** MRI scans. ***Lower Left:*** T1-weighted noncontrast scan. ***Lower right:*** T1-weighted postcontrast scan. The renal cyst (Cy) in the right kidney does not show any enhancement. The lesion (*arrow*) in the left kidney (K) shows marked enhancement, indicating that it is solid in nature. In this example, the contrast-enhanced MRI is superior to CT in the detection and characterization of the left renal mass.



▲ **Figure 6–43.** Comparison of imaging methods: metastatic extra-adrenal familial pheochromocytoma. A 10-year-old boy with hypertension and seizures precipitated by abdominal palpation. Family history of multiple extra-adrenal pheochromocytomas in the mother. ***Upper left:*** Excretory urogram. The right ureter is dilated and elevated (*curved arrow*), with the right posterior portion of the bladder displaced toward the left (*straight arrow*). The urographic diagnosis is possible extra-adrenal paravesical pheochromocytoma. ***Upper right:*** Right femoral arteriogram. Tumor stain (*arrow*) in right paravesical location. The angiographic diagnosis is extra-adrenal paravesical pheochromocytoma. ***Lower left:*** CT scan. Transverse tomogram through bladder (B) shows the tumor (T) indenting the bladder (*arrows*). R = rectum. ***Lower right:*** CT scan. Transverse tomogram through bladder. Recurrence of symptoms following removal of the right paravesical pheochromocytoma prompted another CT study, which shows recurrent tumor (*arrow*) in the bladder wall. Each imaging study complemented or supplemented the previous one. None, however, diagnosed the small liver metastases discovered at surgery.



▲ **Figure 6–44.** Comparison of imaging methods. ***Upper left:*** Example of a nonenhanced computed tomography (CT). ***Upper right:*** Ultrasound study for demonstration of renal calcifications. Fine calcifications in the medullary region indicate medullary nephrocalcinosis. They are of high density on CT (*arrows*) and are shown as echogenic foci (*arrows*) on an ultrasound scan. ***Lower images:*** Examples of a transitional cell carcinoma and the calcified renal cyst. Retrograde urogram (***lower left***) shows filling defects due to tumor in the renal pelvis (*black arrow*) at ureteropelvic junction; also seen are the calcifications in a lower pole mass (*white arrows*). Note that the infundibulum and calices of the lower pole failed to opacify in this 45-year-old woman with hematuria. On the CT scan (***lower right***), the cystic nature of the calcified renal mass (*curved arrow*) is well demonstrated and the CT scan shows better the extent of the tumor (T), which involves the entire lower pole of the kidney and extends into the dilated renal pelvis.



▲ **Figure 6–45.** Comparison of imaging methods. ***Upper images:*** Renal sarcoma with vascular invasion. Axial CT (***upper left***) reveals a left renal mass (*arrow*). The visualized left renal vein is invaded and expanded with thrombus (*asterisk*). On this sagittal ultrasound Doppler image (***upper right***) in the same patient, the thrombus extends across the midline from the left renal vein into the inferior vena cava (IVC) (*asterisk*). ***Lower images:*** Demonstration of an arterial venous malformation to the seminal vesicles. On the CT scan (***lower left***), the right seminal vesicle (SV) is enlarged, but the nature of the enlargement (*arrow*) is difficult to discern. On an MRI scan (***lower right***), the enlarged vessels (*arrows*) are demonstrated as the flowing blood within the vessel and lack signal intensity in contrast to the medium signal intensity of the seminal vesicles (SV). Urinary bladder (B).

BIBLIOGRAPHY

Radiography

Amis ES Jr: Epitaph for the urogram. Radiology 1999;213(3):639–640.

Chan DY et al: Image-guided therapy in urology. J Endourol 2001;15(1):105–110. [PMID: 11248911]

Chapple C et al: Consensus statement on urethral trauma. BJU Int 2004;93(9):1195–1202. [PMID: 15180604]

Dyer RB et al: Intravenous urography: Technique and interpretation. Radiographics 2001;21(4):799–821; discussion 822–824.

Lehnert BE et al: Lower male genitourinary trauma: A pictorial review. Emerg Radiol 2014;21(1):67–74. [PMID: 24052083]

Li X et al: Clinical observation of the adverse drug reactions caused by non-ionic iodinated contrast media: Results from 109,255 cases who underwent enhanced CT examination in Chongqing, China. Br J Radiol 2015;88(1047):20140491. [PMID: 25582519]

McFarlane JP et al: Outpatient ureteric procedures: A new method for retrograde ureteropyelography and ureteric stent placement. BJU Int 2001;87(3):172–176. [PMID: 11167637]

Morey AF et al: Bladder rupture after blunt trauma: Guidelines for diagnostic imaging. J Trauma 2001;51(4):683–686. [PMID: 11586159]

Patel BN et al: Imaging of iatrogenic complications of the urinary tract: Kidneys, ureters, and bladder. Radiol Clin North Am 2014;52(5):1101–1116. [PMID: 25173661]

Sonography

Agrawal A et al: Clinical and sonographic findings in carcinoma of the penis. J Clin Ultrasound 2000;28(8):399–406. [PMID: 10993967]

Ascenti G et al: Complex cystic renal masses: Characterization with contrast-enhanced US. Radiology 2007;243(1):158–165.

Bateman GA, Cuganesan R: Renal vein Doppler sonography of obstructive uropathy. Am J Roentgenol 2002;178(4):921–925. [PMID: 11906873]

Caoili EM et al: Evaluation of sonographically guided percutaneous core biopsy of renal masses. Am J Roentgenol 2002;179(2): 373–378. [PMID: 12130435]

Carmignani L et al: High incidence of benign testicular neoplasms diagnosed by ultrasound. J Urol 2003;170(5):1783–1786. [PMID: 14532776]

Chow L et al: Power Doppler imaging and resistance index measurement in the evaluation of acute renal transplant rejection. J Clin Ultrasound 2001;29(9):483–490. [PMID: 11745858]

Cowan NC: CT urography for hematuria. Nat Rev Urol 2012;9(4):218–226. [PMID: 22410682]

Datta SN et al: Urinary tract ultrasonography in the evaluation of haematuria—a report of over 1,000 cases. Ann Roy Coll Surg Engl 2002;84(3):203–205. [PMID: 12092877]

Fan L et al: Diagnostic efficacy of contrast-enhanced ultrasonography in solid renal parenchymal lesions with maximum diameters of 5 cm. J Ultrasound Med 2008;27(6):875–885.

Frauscher F et al: Comparison of contrast enhanced color Doppler targeted biopsy with conventional systematic biopsy: Impact on prostate cancer detection. J Urol 2002;167(4):1648–1652. [PMID: 11912381]

Hart JL et al: Ultrasound imaging of the scrotum. Br J Hosp Med (Lond) 2008;69(2):M18–M21.

Lu Q et al: Differentiation of renal tumor histotypes: Usefulness of quantitative analysis of contrast-enhanced ultrasound. Am J Roentgenol 2015;205(3):W335–W342. [PMID: 26295670]

Ragheb D, Higgins JL Jr: Ultrasonography of the scrotum: Technique, anatomy, and pathologic entities. J Ultrasound Med 2002;21(2):171–185. [PMID: 11833873]

Sellars ME, Sidhu PS: Ultrasound appearances of the testicular appendages: Pictorial review. Eur Radiol 2003;13(1):127–135. [PMID: 12541120]

Sparano A et al: Using color power Doppler ultrasound imaging to diagnose the acute scrotum. A pictorial essay. Emerg Radiol 2008;15(5):289–294.

Computed Tomography Scanning

Abramson S et al: Impact in the emergency department of unenhanced CT on diagnostic confidence and therapeutic efficacy in patients with suspected renal colic: A prospective survey. 2000 ARRS President's Award. American Roentgen Ray Society. Am J Roentgenol 2000;175(6):1689–1695. [PMID: 11090405]

Boll DT et al: Renal stone assessment with dual-energy multidetector CT and advanced postprocessing techniques: Improved characterization of renal stone composition—pilot study. Radiology 2009;250(3):813–820.

Brown CL et al: Dual-energy CT iodine overlay technique for characterization of renal masses as cyst or solid: A phantom feasibility study. Eur Radiol 2009;19(5):1289–1295.

Caoili EM et al: Delayed enhanced CT of lipid-poor adrenal adenomas. Am J Roentgenol 2000;175(5):1411–1415. [PMID: 11044054]

Caoili EM et al: Urinary tract abnormalities: Initial experience with multi-detector row CT urography. Radiology 2002;222(2):353–360.

Caoili EM et al: Optimization of multi-detector row CT urography: Effect of compression, saline administration, and prolongation of acquisition delay. Radiology 2005;235(1):116–123. [PMID: 15716388]

Eiber M et al: Targeted dual-energy single-source CT for characterisation of urinary calculi: Experimental and clinical experience. Eur Radiol 2012;22(1):251–258. [PMID: 21847542]

Graser A et al: Dual energy CT characterization of urinary calculi: Initial in vitro and clinical experience. Invest Radiol 2008;43(2): 112–119.

Graser A et al: Dual-energy CT in patients suspected of having renal masses: Can virtual nonenhanced images replace true nonenhanced images? Radiology 2009;252(2):433–440.

Hricak H et al: Managing radiation use in medical imaging: a multifaceted challenge. Radiology. 2011;258(3):889–905. [PMID: 21163918]

Israel GM, Bosniak MA: How I do it: Evaluating renal masses. Radiology 2005;236(2):441–450. [PMID: 16040900]

Joffe SA et al: Multi-detector row CT urography in the evaluation of hematuria. Radiographics 2003;23(6):1441–1455; discussion 1446–1455. [PMID: 14615555]

Kawashima A et al: Imaging evaluation of posttraumatic renal injuries. Abdom Imaging 2002;27(2):199–213. [PMID: 11847582]

Mileto A et al: Dual-energy multidetector CT for the characterization of incidental adrenal nodules: Diagnostic performance of contrast-enhanced material density analysis. Radiology 2015;274(2):445–454. [PMID: 25207467]

Primak AN et al: Noninvasive differentiation of uric acid versus non-uric acid kidney stones using dual-energy CT. Acad Radiol 2007;14(12):1441–1447.

Shin SS et al: The sentinel clot sign: A useful CT finding for the evaluation of intraperitoneal bladder rupture following blunt trauma. Korean J Radiol 2007;8(6):492–497.

Szolar DH et al: Adrenocortical carcinomas and adrenal pheochromocytomas: Mass and enhancement loss evaluation at delayed contrast-enhanced CT. Radiology 2005;234(2):479–485. [PMID: 15671003]

Vaccaro JP, Brody JM: CT cystography in the evaluation of major bladder trauma. Radiographics 2000;20(5):1373–1381. [PMID: 10992026]

Magnetic Resonance Imaging

Barentsz JO et al: ESUR Prostate MR Guidelines 2012. Eur Urol 2012;22(4):746–757. [PMID: 22322308]

Claus FG et al: Pretreatment evaluation of prostate cancer: Role of MR imaging and 1H MR spectroscopy. Radiographics 2004;24(Suppl 1):S167–S180. [PMID: 15486239]

Coakley FV et al: Prostate cancer tumor volume: Measurement with endorectal MR and MR spectroscopic imaging. Radiology 2002;223(1):91–97. [PMID: 11930052]

De Rooji M et al: Accuracy of magnetic resonance imaging for local staging of prostate cancer: A diagnostic meta-analysis. Eur Urol 2016;70(2):233–245. [PMID: 26215604]

Fusco R et al: Multiparametric MRI for prostate cancer detection: Preliminary results on quantitative analysis of dynamic contrast enhanced imaging, diffusion-weighted imaging and spectroscopy imaging. Magn Reson Imaging 2016;34(7):839–845. [PMID: 27071309]

Giannarini G et al: Potential and limitations of diffusion-weighted magnetic resonance imaging in kidney, prostate, and bladder cancer including pelvic lymph node staging: A critical analysis of the literature. Eur Urol 2012;61(2):326–340. [PMID: 22000497]

Harisinghani MG et al: Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003;348(25):2491–2499. [PMID: 12815134]

Hricak H et al: The role of preoperative endorectal magnetic resonance imaging in the decision regarding whether to preserve or resect neurovascular bundles during radical retropubic prostatectomy. Cancer 2004;100(12):2655–2663. [PMID: 15197809]

Lim HK et al: Prostate cancer: Apparent diffusion coefficient map with T2-weighted images for detection—a multireader study. Radiology 2009;250(1):145–151.

Mazaheri Y et al: Prostate cancer: Identification with combined diffusion-weighted MR imaging and 3D 1H MR spectroscopic imaging—correlation with pathologic findings. Radiology 2008;246(2):480–488.

McDonald RJ et al: Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015;275(3):772–782. [PMID: 25742194]

Muglia V et al: Magnetic resonance imaging of scrotal diseases: When it makes the difference. Urology 2002;59(3):419–423. [PMID: 11880084]

Mullerad M et al: Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. J Urol 2005;174(6):2158–2163. [PMID: 16280755]

Pretorius ES et al: MR imaging of the penis. Radiographics 2001;21:S283–S298; discussion S298–S299. [PMID: 11598264]

Ryu J, Kim B: MR imaging of the male and female urethra. Radiographics 2001;21(5):1169–1185. [PMID: 11553824]

Seitz M et al: Functional magnetic resonance imaging in prostate cancer. Eur Urol 2009;55(4):801–814.

Shukla-Dave A et al: Detection of prostate cancer with MR spectroscopic imaging: An expanded paradigm incorporating polyamines. Radiology 2007;245(2):499–506.

Takahashi N et al: Small (<2-cm) upper-tract urothelial carcinoma: Evaluation with gadolinium-enhanced three-dimensional spoiled gradient-recalled echo MR urography. Radiology 2008;247(2): 451–457.

Takahashi N et al: MR urography for suspected upper tract urothelial carcinoma. Eur Radiol 2009;19(4):912–923.

Uder M et al: MRI of penile fracture: Diagnosis and therapeutic follow-up. Eur Radiol 2002:12(1):113–120. [PMID: 11868085]

Wertman R et al: Risk of nephrogenic systemic fibrosis: Evaluation of gadolinium chelate contrast agents at four American universities. Radiology 2008;248(3):799–806.

Comparison of Imaging Methods

Andrews SJ et al: Ultrasonography and abdominal radiography versus intravenous urography in investigation of urinary tract infection in men: Prospective incident cohort study. BMJ 2002;324(7335):454–456. [PMID: 11859046]

Bigongiari LR et al: Trauma to the bladder and urethra. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000;215(Suppl):733–740. [PMID: 11429965]

Heidenreich A et al: Modern approach of diagnosis and management of acute flank pain: Review of all imaging modalities. Eur Urol 2002;41(4):351–362. [PMID: 12074804]

Jaffe JS et al: A new diagnostic algorithm for the evaluation of microscopic hematuria. Urology 2001;57(5):889–894. [PMID: 11337288]

Kawashima A et al: Imaging of renal trauma: A comprehensive review. Radiographics 2001;21(3):557–574. [PMID: 11353106]

Lang EK et al: Computerized tomography tailored for the assessment of microscopic hematuria. J Urol 2002;167(2 Pt 1):547–554. [PMID: 11792916]

Lang EK et al: Improved detection of renal pathologic features on multiphasic helical CT compared with IVU in patients presenting with microscopic hematuria. Urology 2003;61(3):528–532.

Nawfel RD et al: Patient radiation dose at CT urography and conventional urography. Radiology 2004;232(1):126–132. [PMID: 15220498]

Sourtzis S et al: Radiologic investigation of renal colic: Unenhanced helical CT compared with excretory urography. Am J Roentgenol 1999;172(6):1491–1494. [PMID: 10350278]

Sudah M et al: Patients with acute flank pain: Comparison of MR urography with unenhanced helical CT. Radiology 2002;223(1):98–105.

Wefer AE et al: Advances in uroradiological imaging. BJU Int 2002;89(5):477–487; Quiz i–iii. [PMID: 11929470]

This page intentionally left blank

7

Vascular Interventional Radiology

Ryan Kohlbrenner, MD; & Roy L. Gordon, MD

Interventional uroradiologic procedures can be divided into two major groups: vascular and percutaneous nonvascular. Percutaneous nonvascular interventional procedures are discussed elsewhere. Regarding vascular interventions, transcatheter embolotherapy is frequently performed to treat urinary tract and pelvic hemorrhage. Embolization is also used for tumor devascularization, for the cessation of renal function, and for the treatment of testicular vein and ovarian vein varices. Balloon angioplasty and stenting of stenotic renal arteries may be performed for secondary hypertension refractory to medical therapy. Renal artery aneurysms may also be treated using catheter-directed techniques such as stent grafting and selective embolization. This chapter will review these and other intravascular interventions.

TRANSCATHETER EMBOLIZATION

Renal AV Fistulas, AV Malformations, and Pseudoaneurysms

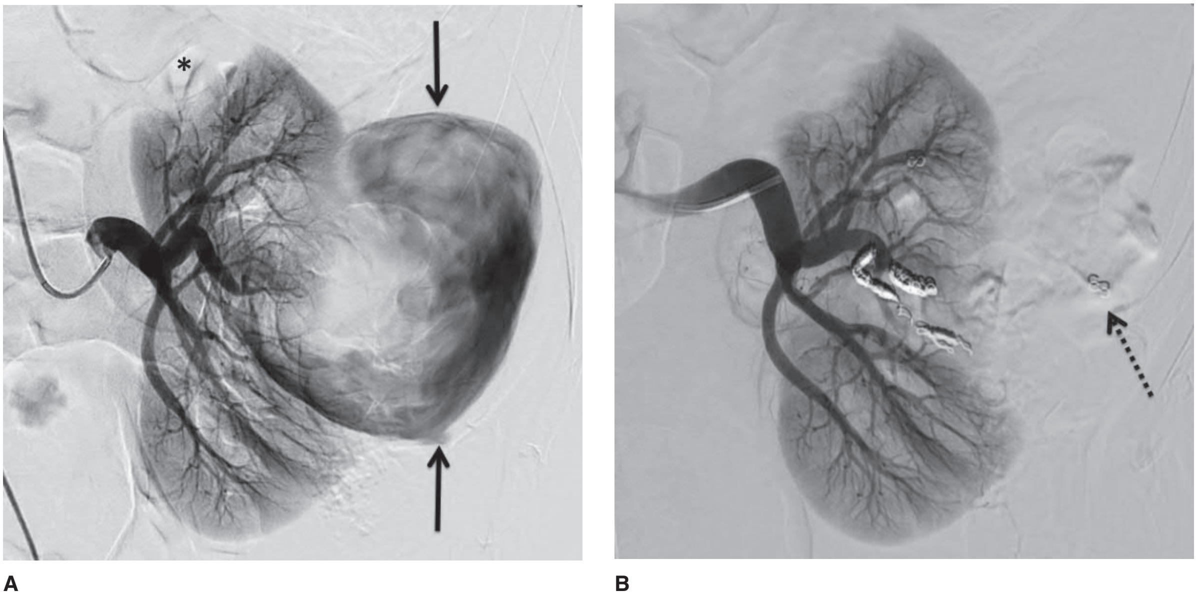
Transcatheter embolization is the treatment of choice for renal arteriovenous fistulae (AVFs), which may be congenital, spontaneous, or acquired. Iatrogenic AVFs are the type most commonly treated by transcatheter embolization. These occur as a complication of such procedures as percutaneous renal biopsy (Libicher et al, 2006), nephrostomy placement, and pyelolithotomy. Trauma or surgery can also result in AVFs. AVF occurring in the transplant kidney is successfully managed by embolization. The classical angiographic finding of spontaneous or acquired AVF is a feeding artery with an early draining vein. Renal pseudoaneurysms may be seen with or without an associated AVF. Psuedoaneurysms, unlike true aneurysms, are not contained by the three normal layers of the arterial wall. In some cases, pseudoaneurysms are contained only by the periadventitial tissues adjacent to a blood vessel. These lesions can be seen not only after biopsy but also after partial nephrectomy. A congenital arteriovenous malformation (AVM) consists of a group of multiple coiled communicating vessels that may be associated with enlarged feeding arteries and draining veins.

The most common clinical presentations are hematuria and retroperitoneal hemorrhage. Congestive heart failure may be seen in patients with large, high-flow AVMs. Hypertension can also occur in the setting of high-volume shunting, as normal renal parenchyma becomes relatively ischemic. Computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) will diagnose and characterize these vascular lesions before angiographic intervention.

Successful intervention requires the angiographic identification, selective catheterization, and embolization of the feeding branches. Using a transfemoral approach, a selective renal angiogram with a 5 French (5Fr) diagnostic catheter is performed to characterize the arteries of the bleeding kidney. In the case of a renal transplant, an initial pelvic angiogram in a steep oblique projection may be useful to characterize the renal artery anastomosis prior to selective injection. A 3Fr or smaller coaxial microcatheter is then used for subselective catheterization and embolization of the feeding artery. Microcoils are used for the occlusion of iatrogenic AVFs and pseudoaneurysms because they can be deployed very precisely in small branches, thereby minimizing the loss of renal parenchyma due to resultant ischemia (Figure 7–1A, B). Inadvertent nontarget embolization and renal artery dissection are uncommon complications of the procedure.

Benign Prostatic Hyperplasia

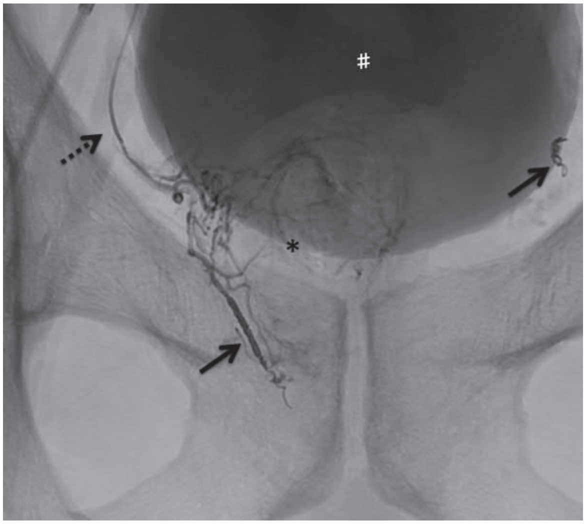
Prostate artery embolization (PAE) has recently emerged as a safe and effective therapy for benign prostatic hyperplasia (BPH). While embolization of the prostatic arteries was historically performed to control refractory bleeding of prostatic origin, recent studies have also demonstrated a reduction in BPH-related lower urinary tract symptoms (LUTS) after PAE (Feng et al, 2017; Uflacker et al, 2916). A 10–15-point reduction in American Urological Association Symptom Index (AUA-SI) scores can commonly be achieved weeks to months



▲ **Figure 7–1.** Transcatheter embolization of a large left renal pseudoaneurysm in a 66-year-old man with hematuria after partial nephrectomy. ***A:*** Selective left renal digital subtraction angiogram (DSA) demonstrates filling of a large pseudoaneurysm (*arrows*) through multiple feeding vessels. An accessory left renal artery accounts for partial nonopacification of the left upper pole (*). ***B:*** Selective left renal DSA after microcoil embolization of multiple arterial feeding branches through a microcatheter shows cessation of flow in the pseudoaneurysm. A single metallic coil (*dashed arrow*) was noted to migrate into the pseudoaneurysm during embolization. Most of the normal renal parenchyma remains unharmed.

after the procedure. Small prospective studies have shown comparable reduction in AUA-SI when compared with transurethral resection of the prostate (TURP) (Carnevale et al, 2016; Gao et al, 2014). However, objective measures of urinary function such as maximum urinary flow rate (Q_{max}) and postvoid residual (PVR) showed greater improvement with TURP (Carnevale et al, 2016). PAE has shown promise specifically in patients with large prostates (>90 g), with reduction in prostate volume by nearly one-third and reduction in AUA-SI by >80% at 3-month follow-up (de Assis et al, 2015). In a small series of patients with chronic indwelling bladder catheters, nearly all patients were able to pass a spontaneous voiding trial within 2 weeks of PAE (Yu et al, 2017). Long-term efficacy data are limited, as PAE is a relatively new procedure. One large cohort study from Europe, however, suggested that symptomatic improvement was sustained in 70% of patients 3–5 years post-PAE (Pisco et al, 2016). Nevertheless, additional comparative studies with longer-term follow-up will be necessary to establish the role of PAE in the BPH treatment paradigm.

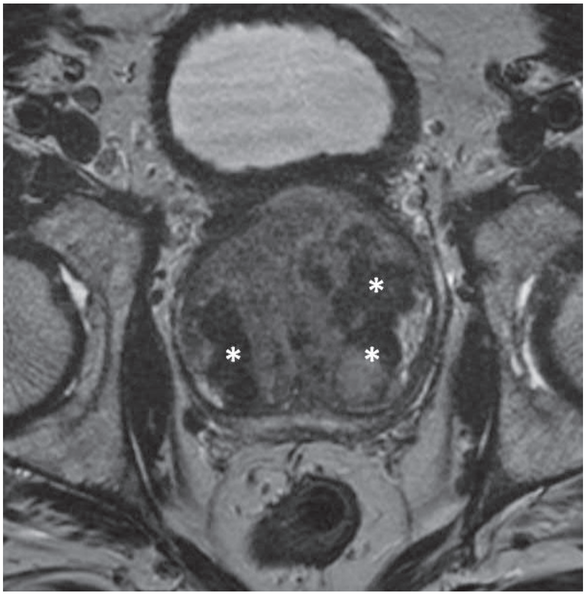
During PAE, the interventional radiologist first achieves arterial access through a transfemoral or transradial approach. Using a 4Fr or 5Fr angiographic catheter, an internal iliac arteriogram is performed in a steep ipsilateral oblique to delineate the arterial anatomy on that side. The small prostatic artery is identified by its anterior course through the lower pelvis, often overlying or near the obturator artery in this projection. The prostatic artery is then catheterized with a coaxial microcatheter (2.5Fr or smaller), and selective angiography is performed to confirm appropriate positioning within the prostatic artery. As collateral branches to the bladder or rectum may be present, cone-beam computed tomography (CBCT) is often performed in the angiography suite to characterize these small extraprostatic tributaries. Many collateral branches can be avoided by further advancement of the microcatheter into the prostatic arteries. Protective coil embolization of extraprostatic collaterals is also considered safe during PAE, as the vascular redundancy within the pelvis will continue to perfuse these extraprostatic tissues through other branches (Bhatia et al, 2017) (Figure 7–2). Embolization of the prostatic arteries is typically performed with tiny particles (100–500 μm) for maximal penetration of the intraprostatic arterial tree. When complete stasis of flow is seen within the prostatic artery, the process is repeated on the contralateral side. Bilateral embolization of the prostatic arteries is necessary to achieve the desired treatment effect (Bihim et al, 2016). Occasionally, patients may have more than two prostatic arteries that require embolization.



▲ **Figure 7–2.** Prostate artery embolization in a 78-year-old man with severe lower urinary tract symptoms. Selective angiogram of the right prostatic artery through a 2.0Fr microcatheter (*dashed arrow*) demonstrates the arterial branches coursing into the right prostatic lobe (*). Protective coils (*solid arrows*) have been placed in the right accessory pudendal and left middle rectal arteries to facilitate safe embolization of the prostatic arteries with particles. The bladder (#) has accumulated a large volume of radiodense urine.

Prostate artery embolization is usually well tolerated and may be performed on an outpatient basis. Nonsteroidal anti-inflammatory medicines are routinely prescribed for 7–10 days after embolization. A course of antibiotics is also typical after post-PAE, as patients are at high risk for urinary tract infection in the days that follow the procedure. Patients may also benefit from short courses of phenazopyridine or oxybutynin for dysuria and bladder spasms, respectively. Patients often experience dysuria and increased urinary frequency for 1–2 weeks after the procedure. Some patients note mild hematuria, hematospermia, or hematochezia, which usually resolves within several days. Postprocedural pain, if present, tends to be mild. Acute urinary retention occurs in approximately 8% of patients, and may necessitate temporary bladder catheter placement until the ischemic edema resolves within the prostate (Uflacker et al, 2016). Injury to extraprostatic tissue such as the bladder or rectum, as a result of nontarget particle embolization, has been reported but is very rare. Impotence, retrograde ejaculation, and incontinence are very uncommon after PAE.

Patients usually note improvement in their LUTS by 2–3 weeks post-PAE, but maximal symptomatic benefit may not be achieved until 3–6 months after the procedure. Necrotic foci throughout the transition zone of the prostate may be appreciated on MRI for several months after therapy (Figure 7–3). For patients with chronic indwelling bladder catheters, a spontaneous voiding trial is often attempted 2 weeks after PAE. If the catheter cannot be permanently removed at that time, a voiding trial at 1 month is recommended. 5-α-reductase inhibitors can often be stopped immediately after PAE in most patients. However, α-blocker therapy is often continued until a symptomatic response to PAE can be confirmed at 1-month follow-up. For those who do not improve or have recurrent symptoms, a prior PAE does not preclude additional urological interventions for BPH.



▲ **Figure 7–3.** Axial T2-weighted MRI images of a 62-year-old man who had undergone a prostate artery embolization approximately 2 months prior. Multiple areas of prostatic necrosis (*) are seen bilaterally.

Pelvic and Lower Urinary Tract Hemorrhage

Transcatheter embolization plays an important role in the management of hemorrhage in the pelvis and lower urinary tract. Embolotherapy to treat renal sources of bleeding is discussed above. Acute life-threatening hemorrhage can occur as a result of trauma, instrumentation, and tumors. Chronic intractable hemorrhage is associated with radiation cystitis, tumors, prostatectomy, and infiltrative disorders. Hemodynamically stable patients should undergo a noninvasive diagnostic study such as contrast-enhanced computed tomography (CT) before embolization. If an arterial bleed is suspected, a CTA followed by a venous phase CT may elucidate the source.

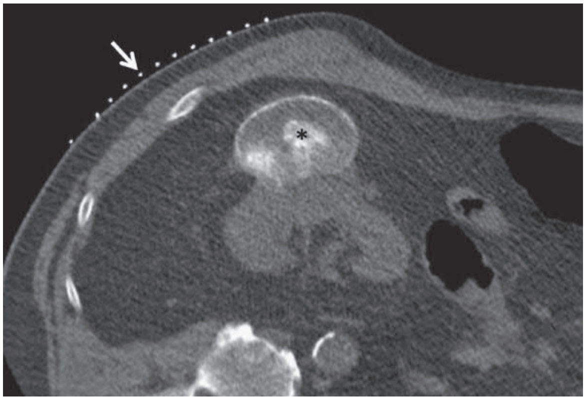
Pelvic fractures resulting in life-threatening hemorrhage require embolization for control if resuscitation and external pelvic fixation have been ineffective. Embolization has been shown to be effective at arresting hemorrhage. Using a transfemoral or transradial approach, the practitioner performs a pelvic arteriogram before selective catheterization and embolization of the internal iliac arteries. Because of contralateral crossover blood supply, pelvic lesions require a thorough investigation bilaterally. Pledgets of absorbable gelatin sponge are frequently used. They can be deployed rapidly, are immediately effective if the patient has a normal coagulation profile, and produce temporary vascular occlusion. Gelatin sponge is easily cut into pieces appropriate to the caliber of the vessel to be embolized. Coils, if used adjunctively with temporary embolics, may hamper future access to the internal iliac artery in the event of rebleeding. Small particulate embolics do not have a role pelvic trauma, as peripheral occlusion of the bleeding vessels may result in ischemia. Complications specific to pelvic embolization are rare with use of absorbable gelatin sponge, unless extensive non-selective embolization is performed bilaterally.

Renal Tumors

A. Renal Cell Carcinoma

Primary renal cell carcinoma (RCC) is treated by surgical excision or thermal ablation. Although its benefits are debated, embolization of the renal artery may be performed prior to radical nephrectomy. The primary goal of preoperative embolization is to reduce intraoperative hemorrhage and allow immediate ligation of the renal vein. Embolization may be beneficial in patients with very large tumors or tumors supplied by many parasitized vessels. The optimal time delay between embolization and surgery is less than 24 hours. Despite the theoretical advantages of preoperative renal artery embolization, no survival benefit has been shown in prospective studies (May et al, 2009). More recently, however, embolization has been used as an adjunctive treatment prior to ablation for large RCC tumors (Woodrum et al, 2019; Yamakado et al, 2006). While prospective studies are lacking, the theoretical benefits of embolization prior to ablation include decreased bleeding during the ablation and, if radiodense embolics are used, improved tumor visualization (Figure 7–4). Preablative embolization also renders the tumor ischemic, potentially making it more susceptible to thermal damage during a subsequent ablation.

Palliation of nonresectable disease that causes pain and hematuria can be achieved by transcatheter embolization (Muller and Rouviere, 2015). Patients with bilateral RCC, and those with RCC in a single kidney, can undergo subselective embolization as an alternative to surgery, thereby sparing normal parenchyma. Embolization of RCC metastases to bone can be performed before surgical resection to decrease intraoperative blood loss (Chatzioannou et al, 2000). CT or magnetic resonance imaging (MRI) may be used for tumor evaluation before and after intervention.



▲ **Figure 7–4.** Noncontrast computed tomographic (CT) images obtained immediately prior to cryoablation probe placement in a 70-year-old man with a 6.5-cm right renal mass. The patient underwent renal mass embolization the day before with ethanol and radiodense ethiodized oil. Despite the noncontrast technique, the margins of the target lesion (*) are now easily identified on CT. A localization grid is seen on the patient's skin (*arrow*).

A transfemoral aortogram and a selective arteriogram are performed to determine the blood supply to the kidney and tumor. An occlusive balloon catheter may be placed within the vessel and inflated before embolization to prevent reflux of embolic material and inadvertent nontarget embolization. However, many physicians use a simple angiographic catheter. Gelfoam slurry or particles are used for embolization prior to nephrectomy. Coils are not used in this setting because they can be dislodged during surgery when the kidney is manipulated. For preablation embolization or palliative embolization of nonresectable tumor, a mixture of ethanol and ethiodized oil is the preferred embolic. RCC bone metastases are embolized by positioning a microcatheter in the vessels supplying the tumor and injecting gelfoam slurry or particles until near stasis in these vessels is achieved.

Tumor embolization is a safe procedure. Complications such as puncture site hematoma and inadvertent nontarget embolization occur in <2% of patients. Many patients, however, experience postembolization syndrome (PES). PES consists of pain, nausea and vomiting, fever, and/or leukocytosis, and likely results from tissue necrosis after successful embolization. Transient ileus, transient hypertension, sepsis, and reversible renal failure have also been described. PES occurs within a few hours of the procedure and may last for several days. Its occurrence should not delay surgical intervention. Tissue swelling and tissue gas formation are seen on imaging studies. Analgesics and antibiotics are used for treatment.

Administration of steroids and antibiotics before embolization may reduce the severity of PES.

B. Angiomyolipoma

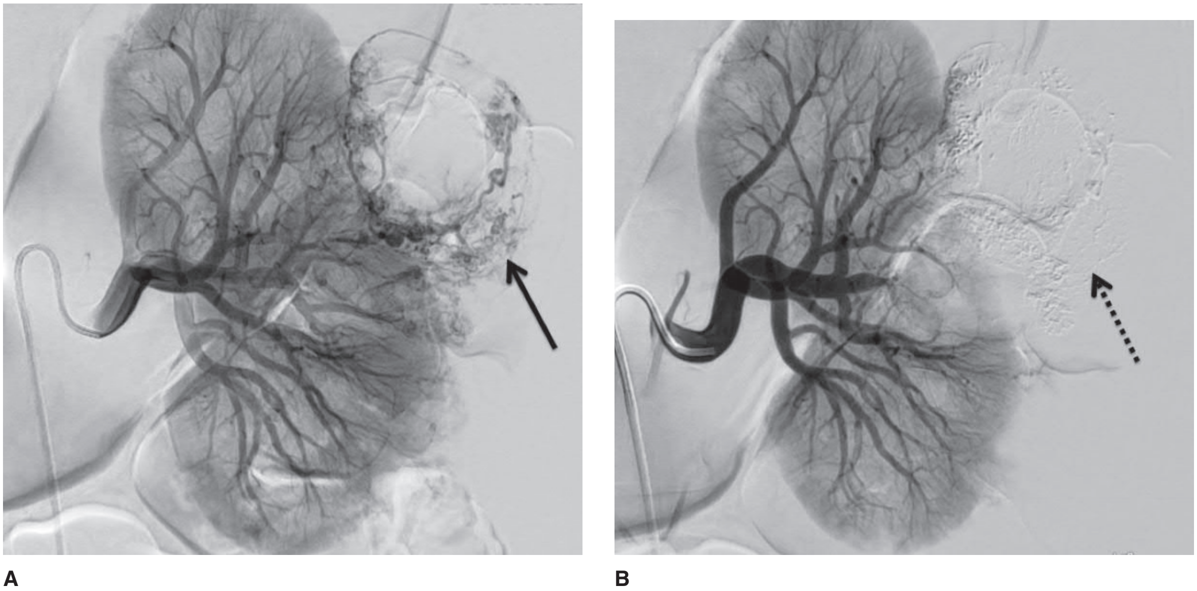
Selective embolization has shown to be an effective method of controlling hemorrhage from benign renal lesions while preserving normal parenchyma (Kothary et al, 2005). This technique has been used to treat actively bleeding angiomyolipomas (AMLs) or to prevent future bleeding in high-risk lesions. Tumors may be multiple or bilateral, as in patients with tuberous sclerosis. In one series, the freedom from surgical intervention at 5-year follow-up was 94% after selective embolization (Ramon et al, 2009). Although prophylactic embolization of AMLs larger than 4 cm in diameter was the norm for many years, this cutoff has recently been called into question (Kuusk et al, 2015). CT or MRI may be used for surveillance of these lesions before or after embolization.

The technique for embolization is similar to that described for RCC. Through a transfemoral or transradial approach, angiography is used to define the arterial supply to the kidney and tumor. The feeding vessels are then selectively catheterized using a coaxial microcatheter. Currently, ethanol and ethiodized oil, mixed in a 7:3 ratio by volume, are the embolics of choice. Ethanol is easy to handle, is inexpensive, and produces permanent occlusion of the vascular bed. Ethiodized oil is radiopaque and therefore is useful for visualizing the flow of the embolic material during the embolization. An occlusion balloon microcatheter may be used to prevent reflux. Ethiodized oil remains within the tumoral vessels, thereby allowing measurement of tumor response on follow-up CT. A completion angiogram is performed to confirm no additional blood flow to the lesion (Figure 7–5A, B).

The reported complications are similar to those seen after RCC embolization. Recurrence of tumor hemorrhage occurs in approximately 10–15% of patients and is treated by repeat embolization. A short-term tapered dose of prednisone may reduce PES after the procedure (Bissler et al, 2002).

Cessation of Renal Function

Total renal infarction using transcatheter embolization may be indicated to cease urine production in certain patients. This includes patients with urinary fistulas, excessive proteinuria, uncontrollable hypertension, or benign obstructive uropathy in poor surgical candidates (De Baere et al, 2000; Toussi et al, 2001). Patients with failed renal allografts and graft intolerance syndrome may also benefit from embolization (Delgado et al, 2005). For patients with end-stage renal disease and intractable hypertension or nephrotic syndrome, the advantages of ablation must be weighed against the risk of diminished erythropoiesis and the loss of fluid regulation in those still producing urine. Total renal ablation must be achieved so that perfusion of surviving parenchyma via



▲ **Figure 7–5.** A 35-year-old woman with a history of tuberous sclerosis and a left renal angiomyolipoma measuring 4.7 cm. ***A:*** Selective left renal digital subtraction angiogram (DSA) demonstrates an exophytic, interpolar renal mass with multiple serpiginous arteries (*arrow*). ***B:*** Repeat angiography after embolization with ethanol and ethiodized oil shows no significant blood flow to the lesion. Embolic material now occupies the tumoral arteries (*dashed arrow*).

pericapsular branches cannot occur. The embolic agent must perfuse the entire renal substance but be safe if it passes through the kidney into the venous circulation. The technique is applicable in adults and children and in both native and allograft kidneys. Renal artery embolization appears to be a safe procedure and is successful in most patients (De Baere et al, 2000).

Available cross-sectional imaging is reviewed prior to angiography to assess for accessory renal arteries. An initial aortogram during the procedure characterizes the renal artery origin(s). Aortography is followed by renal artery catheterization and selective angiography. An occlusion balloon catheter may be used during embolization to prevent reflux to nontarget regions. Embolic microspheres, polyvinyl alcohol, ethanol, or gelatin sponge may be used to embolize the renal arterial tree, with the catheter positioned beyond the origin of the inferior adrenal artery. The procedure is often completed with placement of embolic coils or a vascular plug in the main renal artery.

Postembolization syndrome occurs in most patients and is managed with antiemetics, antipyretics, and analgesics. Inadvertent embolization of the adrenal artery and other visceral vessels is a rare but serious complication that can be avoided by using the occlusion balloon technique. Morbidity and mortality from the procedure are less than those from surgical nephrectomy.

▶ Embolization of Primary Varicocele

The diagnosis and management of varicocele and male infertility are discussed elsewhere. Surgery and percutaneous transvenous embolization appear to be similarly effective in treating varicoceles (Bechara et al, 2009). However, advantages of the percutaneous route include greater patient comfort, ease of bilateral treatment, and reduced recovery time.

The procedure is performed under conscious sedation through a transjugular or transfemoral venous approach. For left-sided varicoceles, a 5Fr angiographic catheter is used to select the left renal vein. The left gonadal vein, often arising from the undersurface of the left renal vein, is subselected with the 5Fr catheter or a coaxially placed microcatheter. The patient is placed in reverse Trendelenburg position, and left gonadal venography is performed. A positive venogram result demonstrates incompetence with filling of collateral vessels. Embolization is often performed with a liquid sclerosant, such as sodium tetradecyl sulfate (STS), or a liquid adhesive, such as *n*-butyl cyanoacrylate. Many operators also place coils within the gonadal vein, commencing at the region of the inguinal ligament, and continuing cranially toward the renal vein, until the gonadal vein and collateral vessels have been occluded. If a right-sided varicocele is also present, the right gonadal vein is selectively catheterized from the inferior vena cava. It is then similarly interrogated and embolized.

The recurrence rate of varicocele after embolization is approximately 4%. Minor complications include contrast extravasation from perforation of the vein, nontarget embolization, venospasm, and hematoma. Patients may experience transient thrombophlebitis if liquid embolics are used.

▶ Embolization of Ovarian Vein Varices (Pelvic Congestion Syndrome)

Pelvic congestion syndrome is a recognized cause of chronic pelvic pain in women that has been associated with lumboovarian vein varices. The pathophysiology has not been entirely elucidated. Symptoms are often worse with fatigue, before menstruation, and in the upright position. Occasionally, vulvar and thigh varicosities are present on examination. In the appropriate clinical context, the diagnosis of pelvic congestion syndrome may be suggested by duplex Doppler ultrasound or magnetic resonance venography. However, pelvic varicosities may also be incidental findings in otherwise asymptomatic women.

Transvenous embolization has produced durable relief of symptoms in most patients (>70%). Most responses occur within 2 weeks of treatment; however, continued improvement has been reported up to 12 months after the procedure (Kim et al, 2006). Through either a transfemoral or a transjugular approach, the ovarian veins are individually catheterized, and embolic agents such as coils, STS, or synthetic glue are deployed in the vessel at the level of the pelvic inlet. Occasionally, embolization of internal iliac vein tributaries may be necessary. Reported complications are similar to those for varicocele embolization. The procedure does not appear to have a deleterious effect on fertility or the menstrual cycle.

▶ Treatment of High-Flow Priapism

High-flow priapism is a rare condition resulting from increased arterial flow into the lacunar spaces of the cavernous tissue. The arteriocavernous fistula most often results from penile or perineal trauma. Color Doppler sonography demonstrates the abnormality.

Transcatheter embolization is an effective, minimally invasive treatment for this condition (Kojima et al, 2009). Pelvic angiography is first used to identify the fistulous lesion. A microcatheter is then advanced through the internal pudendal artery to select the injured vessel. Embolization of the fistula is then performed through the microcatheter. According to recent guidelines, temporary embolic agents such as absorbable gelatin sponge are preferred, as they are less likely to be associated with postprocedure erectile dysfunction (Muneer and Ralph, 2017). Surgery is usually reserved for patients in whom embolization fails.

RENAL ARTERY ANGIOPLASTY AND STENTING

Renal artery stenosis is a common cause of secondary hypertension in adults. Endovascular techniques are the most common means of renal revascularization at present, but there is controversy over the relative benefits of revascularization compared to the most appropriate medical treatment. The ASTRAL (ASTRAL Investigators et al, 2009) and CORAL (Cooper et al, 2014) trials were both large randomized studies comparing renal artery revascularization plus medical therapy with medical therapy alone. Neither study demonstrated any benefit of renal artery intervention when combined with best medical therapy. Nevertheless, both studies have been criticized for their inclusion criteria. For example, nearly two-thirds of patients enrolled in the ASTRAL trial had normal or near-normal renal function, and more than half of the patients enrolled in CORAL had estimated glomerular filtration rates of greater than 60 mL/min/1.73 m^2. More than one-third of the patients in both studies had stenoses of less than 70% (Mohan and Bourke, 2015). Although the benefits of renal revascularization continue to be debated, current American College of Cardiology/American Heart Association guidelines suggest that percutaneous renal revascularization is reasonable in patients with hemodynamically significant stenosis and one of the following: (1) malignant hypertension, (2) resistant hypertension, (3) rapid-onset hypertension, (4) hypertension with small unilateral kidney and no other identifiable cause, or (5) intolerance to antihypertensives (Rooke et al, 2011). In practice, many patients undergoing renal artery PTA and/or stenting have stenoses of >80% with a peak systolic pressure gradient of >20 mm Hg across the lesion and poor response to three or more antihypertensive medicines (Mohan and Bourke, 2015).

Percutaneous transluminal angioplasty (PTA) is the treatment of choice in the management of fibromuscular dysplasia (FMD) with hypertension. The technique involves the use of an inflatable balloon catheter that is positioned endoluminally across the stenosis and then inflated. As these lesions tend to respond well to PTA alone, stenting is not recommended unless a post-PTA complication is noted, such as renal artery dissection. Surgical revascularization is rarely required.

Several diagnostic imaging modalities are used for patient selection and for postprocedure follow-up, including duplex Doppler ultrasound, CTA, and MRA. The advantages and disadvantages of these techniques are beyond the scope of this chapter. Captopril renal scintigraphy is no longer routinely used.

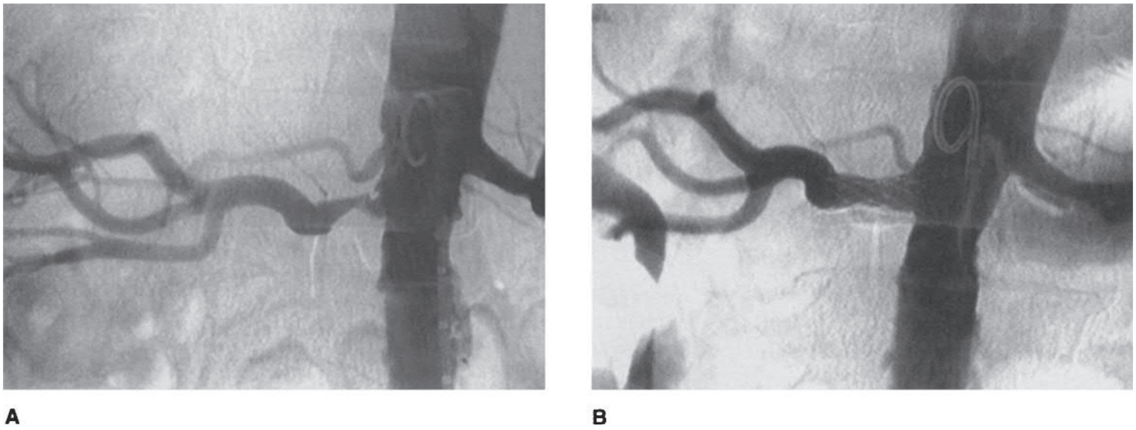
Renal artery stenosis is described as ostial, nonostial (truncal), or branch vessel stenosis. An ostial lesion is located within 3 mm of the aortic lumen and is typical of atherosclerotic vascular disease. In fibromuscular dysplasia, nonostial and branch vessel lesions are more typically seen. The initial technical success rate of PTA varies. It may be as low as 35% for some atherosclerotic vascular disease ostial lesions, but in most series the overall rate approximates 95–100%. Clinical success, as discussed above, is assumed to be highly dependent on patient selection. The best results after PTA have been achieved in hypertensive patients with fibromuscular dysplasia, in whom improvement or cure is achieved in approximately 90%.

Stent placement is usually the method of choice for endoluminal recanalization. Previously, stenting had been reserved for immediate failure or complication of PTA, such as elastic recoil or flow limiting intimal dissection, for residual stenoses of >30%, for a >20 mm Hg peak systolic pressure gradient after PTA, for early restenosis, and for ostial lesions that are difficult to treat by PTA alone. Renal artery stenting results in stabilization (38% of patients) or improvement (30% of patients) of renal function and in durable improvement (49%) or cure (20%) of hypertension (Leertouwer et al, 2000). PTA and stenting have also been used successfully to treat renal allograft artery stenosis. Primary patency rates vary after stenting. The average restenosis rate is approximately 17% after 6–12 months' follow-up. However, the rate increased to 20–30% with longer follow-up. Secondary patency may be achieved in >90% of patients.

Usually, the transfemoral approach is used, although a transradial or transbrachial approach may also be used. Initially, a midstream aortogram is performed to identify the renal arteries, followed by a selective injection to evaluate the morphology and location of the stenosis, the diameter of the vessel, and the percentage of stenosis. In the presence of altered renal function with elevated creatinine levels, carbon dioxide gas may be used as the initial contrast agent. Indicators of a significant stenosis include a reduction of cross-sectional diameter of at least 70%, poststenotic dilatation, collateral vessels to the affected kidney, and a transstenotic systolic pressure gradient of >20 mm Hg across the lesion. Before intervention, an oral antiplatelet agent such as clopidogrel is administered. The patient is heparinized, and a vasodilating agent, such as nitroglycerin, is given via the arterial catheter. Initially, the lesion is crossed with a guidewire. If a high-grade stenosis is present, predilatation with a small balloon may be necessary before definitive angioplasty or stent placement. An outer guiding catheter or sheath is used to facilitate contrast injection during the procedure and to improve catheter stability. Continuous fluoroscopic guidance and "vascular roadmapping" are also used to ensure precision. Balloon-expandable stents are generally preferred because they can be deployed with high precision. The minimal recommended vessel diameter for stenting is 5 mm. A 10–20-mm-long stent is used, and approximately 1–2 mm should protrude into the aortic lumen when ostial lesions are treated (Figure 7–6A, B).

Success of the procedure is defined by <30% residual stenosis and by the resolution of the transstenotic pressure gradient. A percutaneous closure device is frequently used to achieve hemostasis. Aspirin and clopidogrel are continued for at least 6 weeks after the procedure, with aspirin monotherapy continued for 6 months.

The reported complication rate after PTA and stenting varies considerably but ranges from 3% to 10% for experienced operators. Complications include puncture site hematoma; femoral artery pseudoaneurysm; contrast nephropathy; cholesterol embolization; stent malpositioning; and injury to



▲ **Figure 7–6.** Renal artery stenting in an 80-year-old woman with hypertension despite maximal medical therapy and right renal artery stenosis due to atherosclerotic vascular disease. ***A:*** A midstream aortogram at the level of the renal arteries demonstrates a high-grade ostial right renal artery stenosis. ***B:*** Repeat midstream aortogram after placement of a 20-mm-long Palmaz stent, dilated to 6 mm. A widely patent renal artery is seen. The stent protrudes slightly into the aortic lumen. The patient's hypertension improved after the procedure.

the renal artery such as dissection, thrombosis, and rupture. Rarely, procedure-related deaths have occurred. The use of endovascular distal protection devices may reduce the risk of cholesterol embolization during renal artery stenting; these small devices function as filters that trap microemboli dislodged during angioplasty or stent placement.

OTHER ENDOVASCULAR PROCEDURES

▶ Catheter-Based Renal Sympathetic Denervation for Treatment of Resistant Hypertension

Renal denervation is not currently performed in the United States but is available in Europe. The procedure is performed with a specially designed catheter that imparts transluminal radiofrequency energy to the renal artery. This results in destruction of sympathetic nerves within the walls of the renal arteries, inhibiting the renin–angiotensin–aldosterone system and sympathetic activation. After encouraging initial results in smaller studies, a large, randomized, sham-controlled trial known as SYMPLICITY HTN-3 failed to demonstrate a reduction in blood pressure in the denervation group relative to the sham procedure group (Bhatt et al, 2014). Several new denervation devices are currently being investigated, however.

▶ Renal Artery Aneurysms

Renal artery aneurysms are uncommon and are rarely symptomatic. They carry the risk of rupture, with associated life-threatening hemorrhage. Occasionally, they are associated with renovascular hypertension. The indications for treatment of renal artery aneurysms include diameter >2.0 cm, interval enlargement, renovascular hypertension, pain, hematuria, intrarenal thromboemboli, and lesions in women of childbearing age. The diagnosis is made by color Doppler sonography, CT, or MRI.

In the high-risk surgical patient, endovascular techniques may be well suited to aneurysm repair, by excluding the aneurysm while preserving flow to the kidney. Depending on the location of the aneurysm, its relationship to branch vessels, and the presence or absence of an aneurysm neck, the lesion may be amenable to either stent grafting or transcatheter embolization. A stent graft is a metallic stent that is covered by impervious surgical graft material. Its deployment across the aneurysm excludes blood flow to the aneurysm. The cavity of the aneurysm may then thrombose.

Selective embolization of an aneurysm that is supplied by a branch vessel may be performed by placing coils proximally in the branch vessel. This approach results in distal parenchymal infarction and therefore can be safely performed only if there is sufficient renal functional reserve. If there is an identifiable neck separating the aneurysm from the native vessel, coils and a liquid embolic such as ethylene vinyl alcohol copolymer (Onyx) may be used to pack the aneurysm cavity, thereby resulting in thrombosis of the aneurysm while at the same time preserving distal flow. The risks of the procedure are similar to those reported above. Studies comparing surgical repair to endovascular repair report similar outcomes with regard to decline in renal function, mortality, or peri-procedural morbidity (Coleman and Stanley, 2015).

CATHETER-DIRECTED THROMBOLYSIS

This procedure has been used extensively in the peripheral vasculature but only with limited success in the management of native renal artery or aortorenal bypass graft thrombosis. Small series or individual case reports have suggested a possible role in the treatment of recent renal artery occlusion before PTA and for the treatment of acute renal artery thromboembolic disease (Nakayama et al, 2006).

Various mechanical devices are employed to remove clot in addition to or as an alternative to pharmacologic thrombolysis. The diagnosis is made by noninvasive imaging such as duplex Doppler ultrasound, MRA, or CTA and is then confirmed by angiography, at which time fibrinolytic therapy is begun. A diagnostic arteriogram is performed from a transfemoral approach, and an infusion catheter is embedded within the thrombosed segment. Our preferred protocol is continuous infusion of 1 mg tissue plasminogen activator (t-PA) per hour. The patient is monitored for puncture site and systemic bleeding in the intensive care unit throughout the infusion therapy. A repeat arteriogram is performed 12–24 hours after the initiation of therapy. If recanalization can be achieved, an underlying stenotic lesion is often identified, at which time PTA or stenting is performed.

The most feared complication during thrombolysis is spontaneous systemic hemorrhage, and potential contraindications to thrombolysis must be thoroughly evaluated before the procedure. Bleeding may be severe enough to require transfusion or to discontinue the infusion. The incidence of complications is related to the duration of therapy and the dose administered.

BIBLIOGRAPHY

Bechara CF et al: Percutaneous treatment of varicocele with microcoil embolization: Comparison of treatment outcome with laparoscopic varicocelectomy. Vascular 2009;17(Suppl 3):S129–S136.

Bhatia S, Sinha V, Bordegaray M, Kably I, Harward S, Narayanan G: Role of coil embolization during prostatic artery embolization: Incidence, indications, and safety profile. J Vasc Intervent Radiol 2017;28(5):656–664, e3.

Bhatt DL et al: A controlled trial of renal denervation for resistant hypertension. New Engl J Med 2014;370(15):1393–1401.

Bilhim T et al: Predictors of clinical outcome after prostate artery embolization with spherical and nonspherical polyvinyl alcohol particles in patients with benign prostatic hyperplasia. Radiology 2016;281(1):289–300.

Bissler JJ, Racadio J, Donnelly LF, Johnson ND: Reduction of postembolization syndrome after ablation of renal angiomyolipoma. Am J Kidney Dis.2002;39(5):966–971.

Carnevale FC, Iscaife A, Yoshinaga EM, Moreira AM, Antunes AA, Srougi M: Transurethral resection of the prostate (TURP) versus original and PErFecTED prostate artery embolization (PAE) due to benign prostatic hyperplasia (BPH): Preliminary results of a single center, prospective, urodynamic-controlled analysis. Cardiovasc Intervent Radiol 2016;39(1):44–52.

Chatziioannou AN, Johnson ME, Pneumaticos SG, Lawrence DD, Carrasco CH: Preoperative embolization of bone metastases from renal cell carcinoma. Eur Radiol 2000;10(4):593–596.

Coleman DM, Stanley JC: Renal artery aneurysms. J Vasc Surg 2015;62(3):779–785.

Cooper CJ et al: Stenting and medical therapy for atherosclerotic renal-artery stenosis. New Engl J Med 2014;370(1):13–22.

de Assis AM et al: Prostatic artery embolization for treatment of benign prostatic hyperplasia in patients with prostates > 90 g: A prospective single-center study. J Vasc Intervent Radiol 2015;26(1):87–93.

De Baere T, Lagrange C, Kuoch V, Morice P, Court B, Roche A: Transcatheter ethanol renal ablation in 20 patients with persistent urine leaks: An alternative to surgical nephrectomy. J Urol 2000;164(4):1148–1152.

Delgado P et al: Intolerance syndrome in failed renal allografts: Incidence and efficacy of percutaneous embolization. Am J Kidney Dis 2005;46(2):339–344.

Feng S et al: Prostatic arterial embolization treating moderate-to-severe lower urinary tract symptoms related to benign prostate hyperplasia: A meta-analysis. Cardiovasc Intervent Radiol 2017;40(1):22–32.

Gao YA et al: Benign prostatic hyperplasia: Prostatic arterial embolization versus transurethral resection of the prostate—a prospective, randomized, and controlled clinical trial. Radiology 2014;270(3):920–928.

Investigators A et al: Revascularization versus medical therapy for renal-artery stenosis. New Engl J Med 2009;361(20):1953–1962.

Kim HS, Malhotra AD, Rowe PC, Lee JM, Venbrux AC: Embolotherapy for pelvic congestion syndrome: Long-term results. J Vasc Intervent Radiol 2006;17(2 Pt 1):289–297.

Kojima H et al: High-flow priapism undergoing arterial embolization: Review of literature following American Urological Association guideline on the management of priapism. Minim Invasive Ther Allied Technol 2009;18(1):1–5.

Kothary N et al: Renal angiomyolipoma: Long-term results after arterial embolization. J Vasc Intervent Radiol 2005;16(1):45–50.

Kuusk T et al: Treatment of renal angiomyolipoma: Pooled analysis of individual patient data. BMC Urol 2015;15:123.

Leertouwer TC et al: Stent placement for renal arterial stenosis: Where do we stand? A meta-analysis. Radiology 2000;216(1):78–85.

Libicher M et al: Interventional therapy of vascular complications following renal transplantation. Clin Transplant 2006;20(Suppl 17):55–59.

May M, Brookman-Amissah S, Pflanz S, Roigas J, Hoschke B, Kendel F: Pre-operative renal arterial embolisation does not provide survival benefit in patients with radical nephrectomy for renal cell carcinoma. Br J Radiol 2009;82(981):724–731.

Mohan IV, Bourke V: The management of renal artery stenosis: An alternative interpretation of ASTRAL and CORAL. Eur J Vasc Endovasc Surg 2015;49(4):465–473.

Muller A, Rouviere O: Renal artery embolization-indications, technical approaches and outcomes. Nat Rev Nephrol 2015;11(5):288–301.

Muneer A, Ralph D: Guideline of guidelines: Priapism. BJU Int 2017;119(2):204–208.

Nakayama T, Okaneya T, Kinebuchi Y, Murata Y, Iizuka K: Thrombolytic therapy for traumatic unilateral renal artery thrombosis. Int J Urol 2006;13(2):168–170.

Pisco JM et al: Medium- and long-term outcome of prostate artery embolization for patients with benign prostatic hyperplasia: Results in 630 patients. J Vasc Intervent Radiol 2016;27(8):1115–1122.

Ramon J et al: Renal angiomyolipoma: Long-term results following selective arterial embolization. Eur Urol 2009;55(5):1155–1161.

Rooke TW et al: 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58(19):2020–2045.

Toussi H, McConnell C, Srinivasan V: Renal artery embolization for benign obstructive uropathy. J Urol 2001;165(4):1162–1164.

Uflacker A, Haskal ZJ, Bilhim T, Patrie J, Huber T, Pisco JM: Meta-analysis of prostatic artery embolization for benign prostatic hyperplasia. J Vasc Intervent Radiol 2016;27(11):1686–1697, e8.

Woodrum DA, Atwell TD, Farrell MA, Andrews JC, Charboneau JW, Callstrom MR: Role of intraarterial embolization before cryoablation of large renal tumors: A pilot study. J Vasc Intervent Radiol. 2010;21(6):930–936.

Yamakado K et al: Radiofrequency ablation combined with renal arterial embolization for the treatment of unresectable renal cell carcinoma larger than 3.5 cm: Initial experience. Cardiovasc Intervent Radiol 2006;29(3):389–394.

Yu SC, Cho CC, Hung EH, Chiu PK, Yee CH, Ng CF: Prostate artery embolization for complete urinary outflow obstruction due to benign prostatic hypertrophy. Cardiovasc Intervent Radiol 2017;40(1):33–40.

8

Retrograde Instrumentation of the Urinary Tract

Marshall L. Stoller, MD

The ability to manipulate the urinary tract without the need for an open surgical incision differentiates urology from other disciplines. Such intervention may be required for diagnostic or therapeutic purposes (or both). Understanding the various catheters, guidewires, stents, endoscopes, and associated instrumentation is key in helping physicians accomplish their desired tasks. Manipulation of the urinary tract should be performed in a gentle fashion; instruments need not be forced. An understanding of anatomy and alternative instrumentation should allow physicians to accomplish their tasks with finesse. The patient should understand the proposed procedure and potential complications. For example, the attempt to place a retrograde ureteral catheter to drain an infected kidney may ultimately lead to a percutaneous nephrostomy if the surgeon is unable to achieve retrograde drainage. Knowing when to stop is as important as knowing when to start.

Many procedures are performed at the bedside or in a cystoscopy suite under local anesthesia. A patient who is comfortable, informed, and assured will more likely cooperate and tolerate the procedure. A physician who is familiar with the proposed instrumentation and understands its limitations and alternatives will win the patient's confidence.

Manipulation of the urinary tract can result in significant injury. Anticipated prolonged procedures should be covered with appropriate antibiotics directed by preoperative urine cultures and sensitivities. Generous use of a water-soluble lubricant and low-pressure irrigation decreases the likelihood of significant iatrogenic infections. Patient positioning is as important as proper choice of instrumentation. Pressure points must be identified and adequately padded, especially when the patient is placed in the dorsal lithotomy position. In addition, the legs should be secured in their stirrups to prevent accidental injury, such as those that might result from a leg hitting the surgeon after an unexpected obturator reflex during endoelectric surgery.

URETHRAL CATHETERIZATION

Urethral catheterization is the most frequent retrograde manipulation performed on the urinary tract; over 100 million Foley catheters are used annually. Catheters are placed to drain the bladder during and after surgical procedures requiring anesthetics, to assess urinary output in critically ill patients, to collect reliable urine specimens, for urodynamic evaluation, for radiographic studies (eg, cystograms), and to assess residual urine. Such catheters can be left indwelling with a self-retaining balloon, as is done with a Foley catheter. An in-and-out procedure to drain a bladder does not require a self-retaining device. Adequate lubrication and frequency sufficient to keep the bladder at reasonable volumes are critical and must be emphasized to the patient performing self-intermittent catheterization; sterility is secondary. In contrast, when a catheter is left indwelling, it is important to use sterile technique.

Technique of Catheterization

A. In Men

The penis should be positioned pointing toward the umbilicus to decrease the acute angulation as the catheter traverses the bulbar urethra. On most occasions, the catheter passes without difficulty. When difficulties arise, a careful history relating to previous urologic manipulations is critical. Strictures are not infrequent and can occur after endourologic surgery. Urethral strictures can be found from the meatus to the bladder neck. History of a straddle injury may suggest a bulbar urethral stricture. Adequate lubrication injected into the urethra and instruction of the patient to relax his pelvic floor eases the passage beyond the striated rhabdosphincter. A large-caliber catheter of approximately 18Fr (18 French = 6 mm diameter) should be used. Narrow, stiff, small catheters have greater potential of creating false passages and possible perforation. Coudé (elbowed)-tipped catheters frequently help negotiate a high bladder neck, as seen with benign prostatic hyperplasia. With self-retaining Foley catheters, complete advancement until the elbowed valve is at the meatus or until the urine returns is important. Inflating the balloon prematurely (while it is in the urethra) may result in severe pain and possible urethral rupture. This must be emphasized to ancillary nursing personnel dealing with patients who are unable to communicate effectively, because under such circumstances, urethral rupture may present only after severe infection is evident.

B. In Women

It may be difficult to identify the meatus, especially in patients with obesity or hypospadias. Lateral and outward traction on the labia and the use of the posterior bill of a vaginal speculum may be helpful. With adequate instruction and a mirror to visualize the meatus, women can learn to catheterize themselves. For repeat catheterizations, a finger inserted into the vagina can help to guide the catheter.

C. Difficult Placement and Removal

When a urethral catheter cannot be placed, filiforms and followers may be used. The narrow-filiform leaders are stiff and can puncture the urethra if too much force is used. Thus, gentle advancement should stop when resistance is encountered, and the initial filiform should be left in place. A second filiform and a third filiform, and possibly additional ones, should be placed next to the previously placed catheters to ensure that the existing catheter occupies false passages or tortuous kinks. Eventually, one of the filiforms should pass and coil into the bladder. A screw adapter at the end of the filiform can be used to connect progressively larger followers to dilate the narrowed urethra. After adequate dilatation, an open-tipped Council catheter can be placed over the filiform and into the bladder. If a problem or undue resistance is encountered at any stage, the procedure should be aborted and cystoscopic negotiation of the urethra should be undertaken or a suprapubic cystostomy should be placed to achieve adequate drainage.

Indwelling catheters should be secured to a closed gravity drainage system. Drainage tubing connected to catheters should be positioned to limit dependent curls and thereby limit airlocks that will frequently limit bladder evacuation. For long-term requirements in males, the catheter should be secured to the abdominal wall to decrease urethral traction pressure and potential stricture formation. Meatal care is needed to ensure adequate egress of urethral secretions.

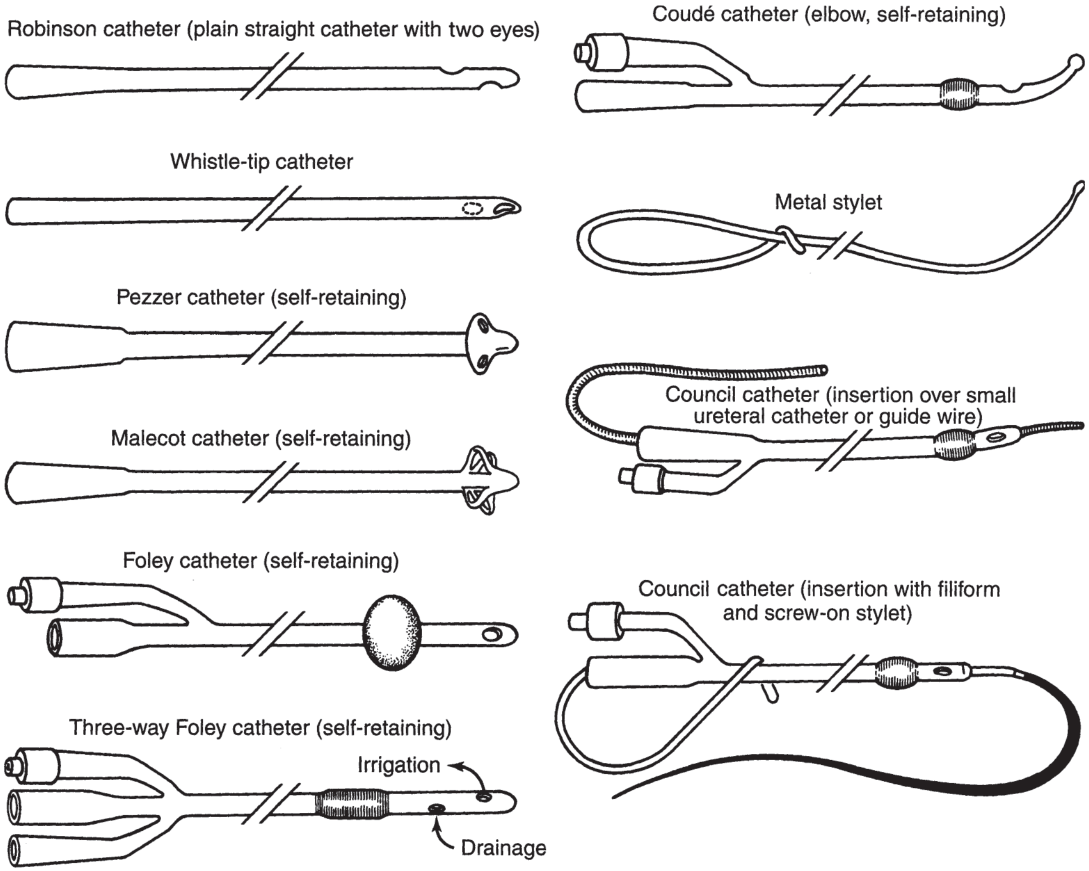
Difficulty is much less common when removing indwelling urethral catheters. Here, the retention balloon is deflated prior to removal. On occasion, the balloon may not deflate. Inspection of the valve frequently reveals a problem. One may cut proximal to the valve in hopes of evacuating the balloon contents, but this is not always successful. Other options include transperineal or transabdominal balloon puncture (which is best with ultrasonographic guidance), or injection of an organic agent such as ether through the balloon port (with a full bladder to prevent chemical cystitis) to dissolve the balloon wall. If the catheter cannot be advanced, retracted, or twisted, one should suspect an unintended suture that could have been placed during prior surgery; such sutures can be cut via the small pediatric endoscope placed along the Foley catheter. Another complication of urethral catheters is incrustation, especially when a catheter is left indwelling for a long time.

Catheter Design

Catheters differ in size, shape, type of material, number of lumens, and type of retaining mechanism (Figure 8–1). Standard sizes of external catheter diameters and most endoscopic instruments are given according to Charriére's French scale (units of 0.33 mm = 1 French [Fr] or 1 Charriére [Charr]). Thus, 3Fr equals 1 mm in diameter and 30Fr equals 10 mm in diameter.

The choice of catheter size is dependent on the patient and the purpose. Large-caliber catheters are used to evacuate blood clots or other debris. Other catheters are used to stabilize grafts after open urethroplasties, for stenting after endoscopic incisions of strictures, for support of external ureteral catheters, or to assess urinary output. Triple-lumen catheters (with one port for balloon inflation and deflation, and one each for inflow and outflow) have smaller lumens than two-way catheters. Other catheter variables include balloon size and construction materials; smaller catheters typically have smaller balloons. Large balloons (eg, 30 mL) can be inflated well over 50 mL to decrease the likelihood of the balloon migrating into the prostatic fossa, especially after transurethral resection of the prostate (TURP). They can be used as traction devices against the bladder neck to control hemorrhage from the prostatic fossa after TURP or holmium laser enucleation of the prostate (HoLEP).

The rigidity of the catheter, the ratio between internal and external diameters, and the biocompatibility depend on the material with which the catheter is made. The standard latex catheter can result in severe reactions in patients with latex allergies, most commonly seen in those with myelomeningoceles. Silicone varieties are good alternatives in such situations. Mucosal irritation is decreased when catheters with a low coefficient of friction are used. Hydromers are placed onto catheters to allow for transient coating, creating an interface between biologic tissues and the foreign catheter; this interface lasts for approximately 5 days. Permanent hydrogel coatings last the life of the catheter. Decreasing the coefficient of friction of these catheters brings about a decrease in mucosal irritation and better biocompatibility. Catheters with a longer-lasting interface result in decreased incrustation.


Robinson catheter (plain straight catheter with two eyes)
Coudé catheter (elbow, self-retaining)
Whistle-tip catheter
Metal stylet
Pezzer catheter (self-retaining)
Council catheter (insertion over small ureteral catheter or guide wire)
Malecot catheter (self-retaining)
Foley catheter (self-retaining)
Council catheter (insertion with filiform and screw-on stylet)
Three-way Foley catheter (self-retaining)
Irrigation
Drainage

▲ **Figure 8–1.** Urethral catheters, metal stylet, catheter, and guidewire techniques for catheter insertion.

URETHROSCOPY

To identify and aid in treating urethral pathology, endoscopic inspection via a urethroscope with a 0° lens is helpful. Stricture disease can be identified or confirmed after radiographic studies. Strictures are characterized by circumferential narrowing. Sequential dilation of urethral strictures by inserting catheters of increasing size exerts shear and tear forces to the mucosa and is likely to produce extended scarring. Thus, stricture recurrence is common if periodic urethral dilation is terminated. Balloon dilation of a stricture with 7–9Fr balloon dilators (which can be passed over guidewires and inflated up to 30Fr with pressures of ≤15 atm) does not exert shear force, but the long-term results are varied. Limited circumferential strictures can be incised under direct vision with an endoscopic cold knife. The incision is usually made at the 12-o'clock position, adequate to allow passage of the urethroscope. The bladder then can be evacuated and adequate irrigation used if further incision results in hemorrhage. It is difficult to identify the true extent and depth of a stricture solely macroscopically because scarring can involve deeper tissues. Here, urethral ultrasonography can be used as an adjunct.

Urethral diverticulum can be identified with urethroscopy. A catheter can be placed through the neck of the diverticulum to help confirm its location during definitive open surgical repair. Urethroscopy can be used to direct injection of dye into rare retained Müllerian duct cysts, to identify and extract foreign bodies or rare calculi, and to access biopsy-suspicious lesions. Urethroscopy allows endoscopic treatment of urethral condylomata.

CYSTOSCOPY

Endoscopic inspection of the lower urinary tract requires irrigation, illumination (fiberoptics), and optics. The optics and illumination are offset by the irrigating and working port. To optimize a complete examination, the rigid endoscope should be rotated, and 0°, 30°, 70°, and 120° lenses may be required. Suprapubic pressure facilitates inspection of the bladder dome, which frequently has an air bubble. A systematic approach is required when evaluating the urethra, prostate, bladder walls, dome and neck, and ureteral orifices (including location, number, shape, and character of efflux). The bladder should be evaluated at different levels of filling. It is only after full distention of the bladder that characteristic glomerulations and ecchymoses are seen in patients with interstitial cystitis. Rectal examination with the endoscope in place is informative, especially in assessing prostate size and length of prostatic urethra. Similarly, concurrent vaginal examination in women can be useful in evaluation of cystoceles.

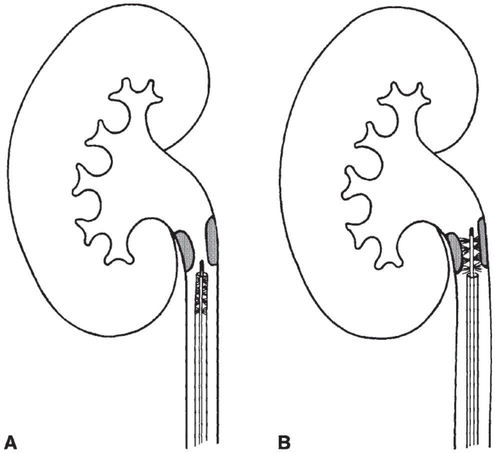
Choice of irrigant during endoscopic manipulation is important. There are conductive and nonconductive irrigants. Conductive irrigants, which include saline and lactated Ringer's solution, would be inappropriate during traditional endoelectric surgery because the electrical charge would be diffused by the irrigant. Nonconductive irrigants include water and glycine. Water has a theoretic advantage of increasing visibility, and because it is hypotonic, it can lyse tumor cells. If the potential exists for increased intravascular absorption, isoosmotic, or other nonhemolyzing agents are preferred to hypotonic solutions.

Rigid endoscopy results in discomfort, which can be minimized with 1% lidocaine per urethra as a local anesthetic. Flexible endoscopes decrease patient discomfort and allow for instrumentation in the supine rather than the dorsal lithotomy position. They are now used routinely in an office setting for hematuria/tumor surveillance and double-J stent retrieval. Videoendoscopy with flexible scopes allows patients to visualize normal and abnormal anatomy and thus helps them understand their pathology. Videoendoscopy reduces fluid contact to the urologist and can help reduce potential cervical neck disease exacerbated by altered posture when endoscopy is performed without videoendoscopic monitoring. However, there are disadvantages. Flexible scopes have smaller irrigating ports, and they do not have a working sheath. As a result, changing lenses, assessing residual urine, and repeat evacuation of irrigant cannot be completed without entirely removing the endoscope. Rigid endoscopy allows for a greater variety of instrumentation, better optics, and increased durability.

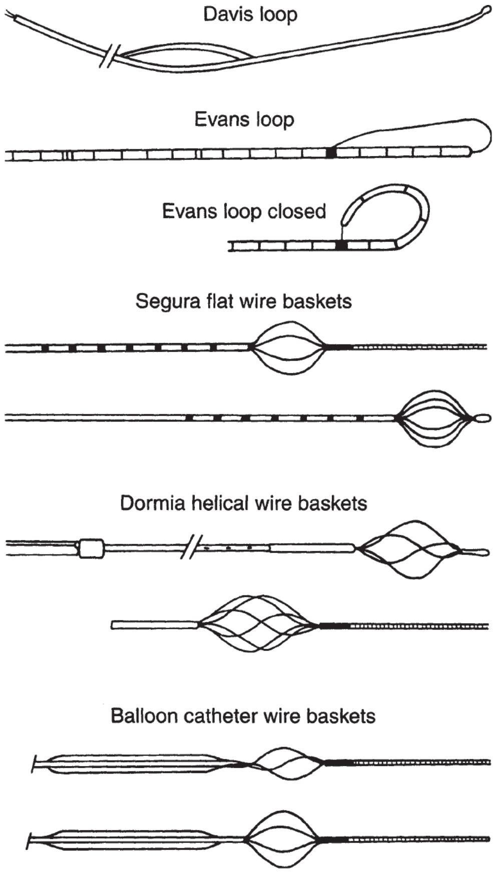
Instrumentation similar to that used to evaluate the urethra and bladder can be used to inspect continent urinary reservoirs or conventional ileal loops. A Robinson or Foley catheter placed prior to the endoscope gives the operator a visual landmark and an exit port for irrigation to keep the procedure at a low pressure. Alternatively, the Foley balloon can be inflated, and the catheter can be plugged to transiently expand the intestinal segment in an effort to identify landmarks or pathologic lesions. Endoscopic inspection allows for identification of calculi, foreign bodies, and mucous plugs and has the potential for intubation of ureterointestinal anastomoses.

URETERAL CATHETERIZATION

Ureteral catheterization is required in performing retrograde pyelography, collecting urine for cytologic examination or cultures, and performing brush biopsies (Figure 8–2). Other procedures (Figure 8–3) that require ureteral catheterization



▲ **Figure 8–2.** Brushing of a proximal ureteral lesion. ***A:*** Insertion of the brush covered by a catheter. ***B:*** Advancement of the brush through the lesion.

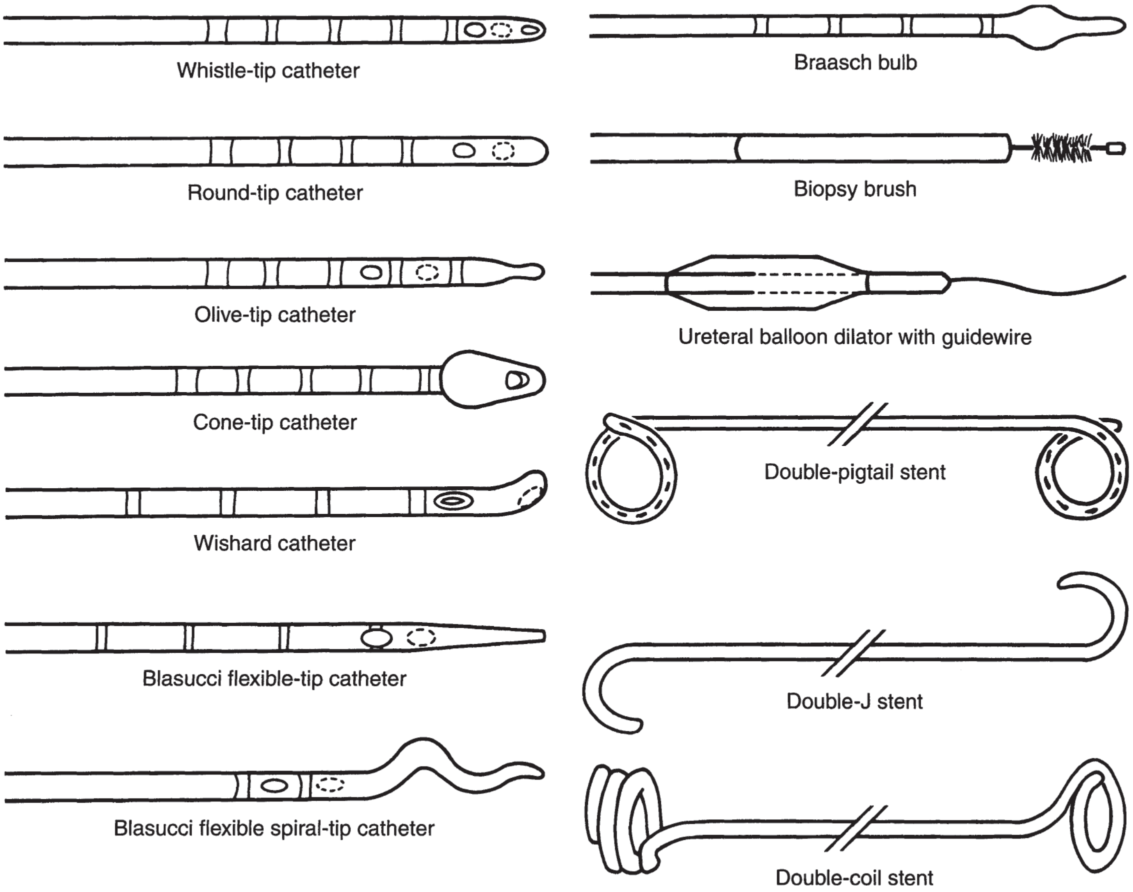


▲ **Figure 8–3.** Loops, wire baskets, and wire baskets with balloon catheters for extraction of ureteral stones.

include draining an obstructed kidney due to either intrinsic or extrinsic compressions and placement of an internal double-J stent. Finding the ureteral orifice can be difficult. Long-term indwelling Foley catheters, infection, history of ureteral reimplantation, or renal transplantation can hinder identification of the ureteral orifice. One must first try to identify the interureteric ridge and then look for a jet of urinary efflux. Varying bladder volumes and use of intravenous methylene blue may be helpful. However, it may take up to 5–20 minutes for intravenous agents to be excreted out of the ureteral orifice. Once the orifice is identified, catheters usually are placed uneventfully. However, in the setting of benign prostatic hyperplasia with J-hooking of the distal ureter, previous retroperitoneal surgery, reimplantation of the ureter, decreased lower extremity mobility or other skeletal abnormalities, or edema or kinking secondary to longstanding impacted ureteral calculi, catheterization procedures can be difficult or impossible. An Albiron bridge may help direct catheters and guidewires. Alternatively, using an angiographic exchange catheter with an angle-tipped hydrophilic guidewire allows for a relatively atraumatic approach to identify and manipulate the ureteral orifice.

There are many configurations of catheter tips (Figure 8–4). Acorn or cone-tipped catheters are excellent for routine retrograde pyelography. Care should be taken to eliminate air in the catheter before injection to avoid confusing air with a filling defect. Fluoroscopy helps determine the appropriate volume of radiocontrast material to decrease the likelihood of pyelolymphatic or pyelovenous reflux or forniceal rupture. The average collecting system holds 7–9 mL of contrast material. If performed under local anesthesia, overdistention is recognized by severe ipsilateral flank pain. With low-pressure injections, there is no systemic absorption of contrast material. A coudé-tipped catheter allows for dramatic mobility of the tip of the catheter by merely twisting it; there is no need for exaggerated motion of the endoscope. This is helpful in orifices that are difficult to identify because of edema or tumor infiltration.

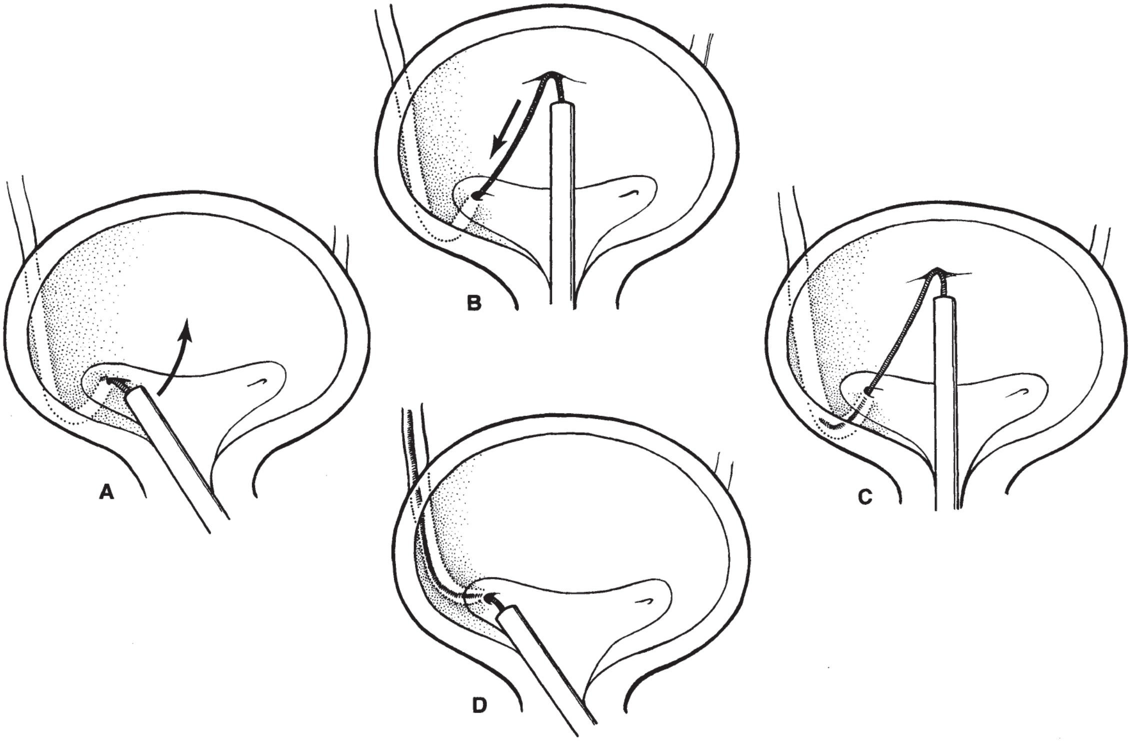
To bypass severe angulations, passage of a guidewire must first be attempted. Straight guidewires can be made floppy



▲ **Figure 8–4.** Ureteral catheters and self-retaining internal stents.

if they have retractable cores, and this allows easy passage frequently. At times, hydrophilic coudé-tipped torque guidewires are helpful. If the orifice can be engaged with the tip of the guidewire but the guidewire cannot be advanced, the tip of the endoscope should be pivoted toward the contralateral orifice while the guidewire is advanced through the endoscope just enough to keep the guidewire engaged in the orifice. The guidewire should then be advanced against the back wall of the bladder, effectively changing the vector force so that the wire can be advanced through a severe J deformity (Figure 8–5). With the guidewire advanced, an exchange catheter can be advanced over the guidewire for injection of contrast material, to be exchanged later for another (and frequently more rigid) guidewire or an open-ended catheter. A coudé-tipped guidewire or floppy-tipped guidewire (with a removable core guide) can be advanced through such exchange catheters to facilitate bypassing stones or severe kinks. A push–pull maneuver (pulling the exchange catheter while pushing the guidewire) frequently straightens the ureter as a result of resistance from the exchange catheter, allowing advancement of the guidewire. To increase resistance, an occlusion balloon ureteral catheter can be inflated and with gentle traction can help straighten a kinked or tortuous ureter. Additional helpful maneuvers include deep exhalation, thus elevating the diaphragm, external cephalad pressure by an assistant, or Trendelenburg patient positioning.

Double-J catheters are used to facilitate internal drainage due to obstruction from ureteral angulation and internal or external ureteral compression; they are also used to help decrease the likelihood of sepsis or obstruction in the presence of steinstrasse after extracorporeal shockwave lithotripsy. Double-J stents increase the internal lumen of the ureter. This increase may be used to one's advantage in the setting of a narrow ureter. Placing a double-J catheter and postponing the ureteroscopy for a few days significantly decreases the difficulty of the subsequent procedure. Double-J stents disrupt normal ureteral peristalsis. These stents can be placed over a guidewire or with a closed leading end. With proper placement of the proximal end into the renal pelvis, the J should project in the lateral position when seen on fluoroscopy or x-ray. Projection in an anterior–posterior position suggests a proximal ureteral location. Proximal-J stent placement can be confirmed by renal ultrasonography during placement in pregnant patients. If it is too long, the distal end in the bladder can result in severe irritative voiding symptoms; if it is too short, it is more likely to migrate



▲ **Figure 8–5.** Negotiating a difficult ureteral orifice. ***A:*** Guidewire engaged in orifice cannot be advanced. ***B:*** Endoscope is rotated toward contralateral orifice. Guidewire remains engaged in orifice. ***C:*** Guidewire is advanced against bladder wall. ***D:*** Guidewire negotiated beyond angulation.

proximally beyond the ureteral orifice into the ureter. In the latter situations, drainage cannot be ensured, and the stent must be extracted with a ureteroscope or snared with a ureteral stone basket.

Patients must be informed that internalized stents have been placed. Frequently, they will not feel the stent. When the stent is left in place for prolonged periods, the likelihood of incrustations, poor drainage, and difficult extraction is increased. It is unclear whether double-J stents facilitate drainage because of drainage around the catheter or via the numerous side holes communicating with the internal lumen. New helically ridged double-J ureteral stents likely enhance ureteral stone passage through unidirectional ratchet-like motion over the external ridges during respiratory and body wall motion. Metal stents have been used for long-term placement and can be left indwelling for one year. Other complications include distal migration into the bladder, distal migration beyond the bladder neck (resulting in total urinary incontinence), and flank pain during micturition secondary to reflux. The catheter can be removed with forceps via a flexible or rigid cystoscope or by pulling a string that has been attached to the distal end of the catheter and left exiting through the meatus. Although double-J catheters have potential complications, they can help ensure internal urinary drainage without the need for a percutaneous nephrostomy tube.

Balloon dilators can be used to ease passage of ureteroscopes (rigid or flexible; see Chapter 8) and extract intact large calculi. Balloons are routinely passed over a guidewire. Woven balloons have a tight, unfolded outer surface that shortens in longitudinal length when inflated. In contrast, nonwoven varieties are folded and may be difficult to pass after initial inflation and deflation; however, they do not shorten in length with inflation. Balloons inflated alongside distal ureteral calculi can result in balloon perforation or extrusion of the calculus outside the ureteral lumen. Balloon inflation is best achieved with ratcheted or torqued syringe aids directed with pressure gauges. Ureteral access sheaths, frequently made with a hydrophilic coating, can be placed over a guidewire. They dilate the ureter without the need for a ureteral balloon and simplify multiple passages up the ureter.

Retrograde endopyelotomy is an alternative to laparoscopic and open surgical repair, and percutaneous antegrade approaches. After documentation of the exact location of the ureteropelvic junction obstruction under fluoroscopic control, a 150-cm superstiff Lunderquist guidewire is advanced into the renal pelvis. The endoscope is removed, the retrograde ureteroscope is advanced, and laser incision can be made under direct vision. Successful results are seen in approximately 70% of patients. An internal endopyelotomy double-J stent, 14Fr at the proximal end, straddling the ureteropelvic junction, and tapered to 6–8Fr as it enters and coils in the bladder, or a routine 7–8Fr double-J ureteral stent is placed over the stiff guidewire and left in place for 6 weeks.

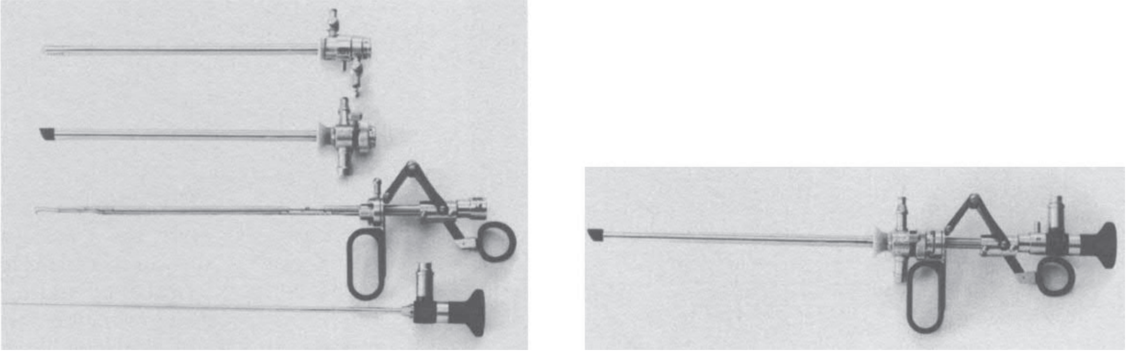
A large selection of endoscopic baskets is available to entrap and remove material including calculi, sloughed papillae, bulky tumors, fungal bezoars, and foreign bodies. Baskets are designed with and without filiform leaders and can be advanced on their own or, more commonly, through the working ports of flexible and rigid ureteroscopes. Round wire baskets can be torqued to help entrap the target material. A few (two or three) wired baskets are used for large material, while slightly more (four to six) wired baskets are used for small or numerous objects. Flat-wired baskets can engage stones effectively. If twisted, however, the wire can fold and transform into a knifelike edge. Once the basket is engaged, one should ensure that the endothelium is not entrapped. Gentle traction helps extract these foreign materials. Engaged baskets may be difficult to disengage. Occasionally, one must cut the handle and place a ureteroscope alongside the basket to facilitate stone and basket extraction. Nitinol baskets have rounded tops and decrease potential endothelial trauma and are now the basket of choice for most urologists.

Transurethral injections can be performed through a variety of endoscopes. Newer injectables include fibrin glue, Botox, and bulking agents for deflux procedures.

TRANSURETHRAL SURGERY

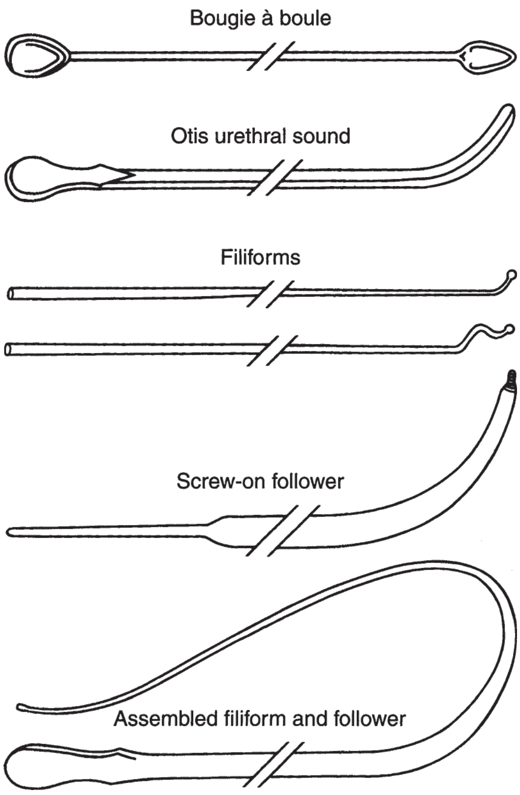
Resectoscopes are endoscopes with sheaths of 10–30Fr (Figure 8–6) designed for transurethral surgery; they allow urologists to excise, fulgurate, or vaporize tissue from the lower genitourinary tract. Applying an alternating current at high frequencies decreases muscular contractions and allows for cutting and coagulation properties. A pure sinewave is optimal for cutting, whereas dampened oscillating waveforms are best for coagulation. It is possible to combine the two waves to allow for simultaneous cutting and coagulation. A ground plate, as an indifferent electrode, usually applied over the hip, is required. The cutting current results in rapid vaporization of tissue, allowing the cutting loop to move easily through tissue with minimal resistance, and separates the chip, enabling easy flow into the bladder. Rapid succession of cutting sweeps allows rapid surgical excision. In contrast, a coagulation current results in less rapid vaporization and thus decreased separation of tissue from the cutting current. If a traditional resectoscope does not cut tissue, the operator should check for a broken resecting loop, a broken or disconnected cable or generator, or a conductive irrigant (as with saline) that diffuses the current. In contrast, plasmakinetic or bipolar resectoscopes send current from one edge of the endoscopic loop to the other. A high electrical current is generated locally at the loop and effectively vaporizes tissue on contact. Because of the bipolar design, conductive irrigants are used with these bipolar resectoscopes. Resection can also be performed with lasers in a similar fashion.

Before transurethral surgery, the urethra should be calibrated with sounds to ensure ease in placing the resectoscope. Urethral sounds and probes come in numerous



▲ **Figure 8–6.** Transurethral resectoscope. ***Left:*** Continuous-flow sheath, standard sheath, working element with cutting loop, telescope. ***Right:*** Instrument assembled.

varieties (Figure 8–7). An Otis urethrotome can be used to incise the urethra at the 12-o'clock position, thereby decreasing the potential for stricture disease in narrow urethras. Generous use of a water-soluble lubricant is indicated. Before placement of the resectoscope, the loop should be inspected for defects and for appropriate engagement to ensure complete retraction into the sheath, thereby allowing resected tissue to flow easily into the bladder. The endoscope can be placed under direct vision, especially if the patient has not recently been cystoscoped. Alternatively, a Timberlake obturator allows for blind placement of the resectoscope sheath. Older endoscopes require the operator to intermittently remove the working element to allow evacuation of bladder contents. Contemporary endoscopes have an additional channel for continuous operation. An alternative is a percutaneous suprapubic drainage catheter, which allows for maximal continuous flow. Orientation with identification of landmarks, such as the verumontanum and the ureteral orifices, before resection dramatically decreases the potential for complications. Bladder lesions are best resected with minimal bladder distention to decrease the likelihood of perforation. A Bugbee electrode can be used for point coagulation of bleeding points or pathologic lesions. A rollerball can be used to coagulate large areas. Transurethral resection can be used to resect an obstructing prostate gland, to drain prostatic abscesses, or to unroof the ejaculatory duct in select infertility patients.



▲ **Figure 8–7.** Urethral probes and sounds.

Transurethral resection of the prostate (TURP) is a time-tested procedure for resecting prostatic tissue and decreasing symptoms of urinary obstruction. In experienced hands, this can be done with minimal complications. Holmium laser enuleation of the prostate (HoLEP) is now being popularized and allows for complete enucleation of the prostatic adenoma. With appropriate endoscopic countertraction and the use of high-power lasers, the adenoma can be enucleated and then can be morcellated and evacuated in a safe fashion. New, alternative procedures are being investigated, especially with patients who are poor anesthetic risks, whose life expectancy is limited, or who are averse to TURP. Those with small glands or with bladder neck contractures have been treated by transurethral incision of the prostate from a point just distal to the ureteral orifices to the verumontanum.

Transcystoscopic urethroplasty, also known as **prostatic balloon dilatation**, dilates the prostatic urethra under visual and fluoroscopic control. Intraurethral coils can be placed in high-risk patients to avoid permanent catheter drainage; however, if these coils need to be removed, they can be quite bothersome. Thermotherapy treatment delivers temperatures of 41–44°C for 60 minutes. Obstructing median lobes are unsuited for such techniques. Interstitial laser ablation of the prostate gland is another method for the management of prostatic enlargement. A variety of bipolar systems are available that allow for vaporization of prostatic tissue. Hemorrhage is limited compared to formal resection techniques and takes longer to remove an equivalent amount of tissue. Many alternative techniques are becoming popular alternatives to the TURP in the management of benign prostatic hyperplasia.

There are various cutting techniques for resecting an obstructing prostate gland during TURP, HoLEP, or other procedures. All require good vision, a comfortable operator, identification of the surgical capsule, and established goals that are met before starting additional stages of the procedure. Pulsatile arterial bleeders should be coagulated first and venous hemorrhage next. Occasionally, arterial bleeders cannot be coagulated without additional resection of tissue. An Ellik bulb or piston syringe should be available to evacuate resected tissue. At the conclusion of the procedure, one should ensure adequate resection and hemostasis, and perform an inspection for forgotten chips of tissue and possible injuries. A Foley catheter should be placed into the bladder and irrigated to confirm unobstructed flow and adequate hemostasis. If an undermined trigone is suspected, a coudé-tipped catheter, a finger in the rectum, or a stylet inserted into the catheter can help in proper placement. The Foley balloon should be inflated 20 mL + 1 mL for each gram of resected tissue. Gentle traction on the catheter can aid hemostasis.

Videocameras are routinely attached to the optical eyepiece while transurethral surgery is performed. Use of the camera helps to reduce the risk of cervical disk disease and to distance the surgeon from blood products. It is an excellent resource to improve the teaching of endoscopic surgery.

Acute complications include intra- or extraperitoneal rupture of the bladder, rectal perforation, incontinence, incision of a ureteral orifice with possible reflux or stricture, hemorrhage, gas explosion (especially during resection of a bladder lesion at the dome in the presence of accumulated gas), epididymitis, sepsis, and transurethral resection syndrome. The transurethral resection syndrome is characterized by delusional hyponatremia resulting in possible confusion, congestive heart failure, or pulmonary edema. It is secondary to a large amount of fluid being absorbed, usually through a perforation of a low-pressure system such as the venous sinusoids. If perforations are noted, especially into a sinus, the height of the irrigating solution should be lowered, hemostasis achieved, and the procedure brought to a rapid conclusion. Other complications include impotence (with excessive coagulation) and urethral stricture disease. After an adequate prostatic resection, retrograde ejaculation almost always occurs.

LOWER TRACT CALCULI

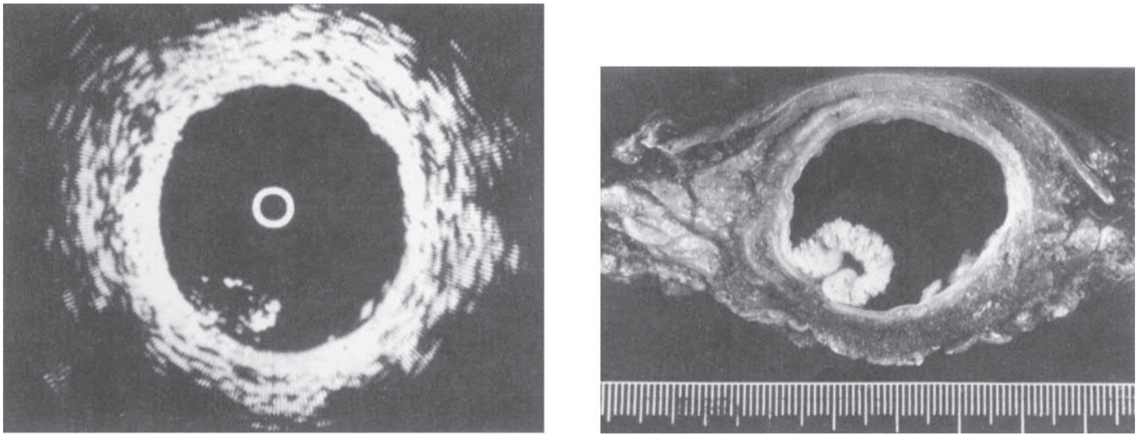
Most bladder calculi originating from the upper tract pass spontaneously through the urethra. In contrast, bladder calculi resulting from outlet obstruction may require endoscopic extraction. Many of these calculi can be washed out or extracted with the aid of various forceps or a resectoscope loop. Calculi too large to pass through an endoscopic sheath first require fragmentation. Visual lithotrites with crushing jaws or a punch-type mechanism are effective. Introduction of these bulky devices is potentially dangerous. A distended bladder facilitates effective engagements of the stone without injuring the bladder wall. Twisting the lithotrite before crushing ensures that the bladder wall is free from the instrument.

Other methods available to fragment bladder calculi include ultrasonic, electrohydraulic, laser, and pneumatic lithotrites. Ultrasonic lithotrites use vibratory energy delivered via a rigid metal transducer. An offset endoscopic lens is required. Gentle pressure of the transducer against the stone facilitates fragmentation; excessive pressure can erode or perforate the bladder wall. A hollow core with suction extracts the fragments. Electrohydraulic lithotripsy generates a spark gap, resulting in a shockwave. It is delivered at the end of a flexible catheter and can be applied as single or repetitive shocks. Fragmentation can be performed with normal saline. A rheostat can adjust the power output. A high setting can result in the stone caroming to various locations in the bladder; lower settings result in suboptimal fragmentation. To optimize fragmentation, the tip of the lithotrite should be a few millimeters away from the stone. To protect the endoscopic optics, the endoscope should be kept at a distance. Shockwaves fragment brittle material, such as the stone or a lens. Biologic tissues are elastic and are unharmed provided the spark gap does not touch them. Air-driven, jackhammer-like devices (rigid and flexible) can be used for stone fragmentation. Pneumatic lithotrites are effective with minimal tissue trauma. They use reusable probes and are powered by compressed gas. The photothermal mechanism of holmium lasers is effective in fragmenting all types of stones—large, small, and multiple bladder stones—and is now the most popular lithotrite. Uric acid calculi produce small amounts of cyanide gas when fragmented with holmium lasers; no clinical sequelae have been documented.

ADVANCED INSTRUMENTATION

▶ Lasers

Lasers (light amplification by stimulated emission of radiation) have been used through flexible and rigid endoscopes. Carbon dioxide and argon lasers result in tissue penetration that is inadequate for the needs of urology. Neodymium:YAG



▲ **Figure 8–8.** Multifocal bladder cancer. ***Left:*** Transurethral ultrasound. ***Right:*** Cystectomy specimen.

(yttrium aluminum garnet) lasers give adequate tissue coagulation and are useful for various lesions. The holmium:YAG system is excellent for stone fragmentation and tissue ablation and is now the most popular system in use. Disadvantages are the lack of adequate tissue for histopathologic evaluation and the initial cost of machinery.

Ultrasonography

Ultrasound has found increased application to the lower genitourinary tract. It results in minimal discomfort; gives a three-dimensional appreciation of the shape, size, and volume of organs and disease; and can provide direct intervention. Various transducers are available; high-megahertz transducers are required for superficial structures (for example, scrotal structures) to assess testicular disease (including tumors and torsion), while low-megahertz transducers are reserved for deep structures (eg, guiding percutaneous access for kidneys and bladders). Intervening tissue can significantly reduce image quality.

Transrectal ultrasound is valuable in evaluating the prostate to determine size and to confirm digital information or survey the prostate on the basis of an elevated prostate-specific antigen (PSA) to help determine the presence and stage of a suspected malignant tumor. Because of the low incidence of detecting malignancies (1.6–7%), mass screening programs are not cost-effective. Direct needle biopsies, with automatic biopsy mechanisms, are quick, well tolerated, and result in reliable tissue cores and less pain than traditional needles (such as Tru-Cut) directed under digital palpation. Percutaneous drainage tubes, radioactive seed implants, and temperature coils used for cryosurgery of the prostate can be placed safely under transrectal ultrasonic guidance. Transrectal ultrasonography can yield unreliable images that often are misinterpreted by the novice. Pitfalls include faulty instrument settings, poor coupling caused by feces or gas, and unrecognized artifacts resulting from reverberation, deflection, shadowing, or enhancement.

Suprapubic ultrasonography can help assess prostate anatomy, especially size and intravesical extension. It can help evaluate the bladder for residual urine and for calculi that are questionable on plain abdominal radiographs. (Changing the patient's position can shift the position of a calculus.) Distal ureteral stones can be identified, especially when visualized through a full bladder used as an acoustic window. Double-J stents, incrustations, diverticula, and large malignant lesions can be identified. The procedure also can direct placement of suprapubic cystostomy drainage catheters.

Additional applications include endocavitary, color, Doppler, and dynamic ultrasonography. Endocavitary ultrasound, which includes transvaginal, transurethral (Figure 8–8), and transcystoscopic techniques, can delineate vaginal, urethral, and bladder disease. Endoureteral ultrasound can help in the identification of crossing vessels, preferably before an endopyelotomy. Color and Doppler ultrasound can assess blood flow as related to erectile dysfunction. Dynamic ultrasound can supplement urodynamic findings. Ultrasound applied to the lower genitourinary tract causes minimal discomfort and provides valuable information.

BIBLIOGRAPHY

Urethral Catheterization

Bloom DA et al: A brief history of urethral catheterization. J Urol 1994;151:317.

Cardenas DD et al: Intermittent catheterization with a hydrophilic-coated catheter delays urinary tract infections in acute spinal cord injury: A prospective, randomized, multicenter trial. PM&R (Physical Medicine and Rehabilitation) 2011;3(5):408–417.

Choong S et al: A prospective, randomized, double-blind study comparing lignocaine gel and plain lubricating gel in relieving pain during flexible cystoscopy. Br J Urol 1997;80:69.

Christison K et al: Intermittent catherization: The devil is in the details. J Neurotrauma 2017.

Foxley S: Indwelling urinary catheters: Accurate monitoring of urine output. Br J Nurs 2011;20(9):564, 566–569.

Lapides J et al: Clean, intermittent self-catheterization in the treatment of urinary tract disease. J Urol 1972;107:458.

Lee EA, Malatt C: Making the hospital safer for older adult patients: A focus on the indwelling urinary catheter. Perm J 2011;15(1):49–52.

Mamoulakis C et al: Results from an international multicentre double-blind randomized controlled trial on the perioperative efficacy and safety of bipolar vs monopolar transurethral resection of the prostate. BJU Int 2012;109(2):240–248.

Williams JC et al: Deflation techniques for faulty Foley catheter balloons: Presentation of a cystoscopic technique. Tech Urol 1996;2:174.

Transrectal and Transurethral Ultrasound

Demura T et al: Differences in tumor core distribution between palpable and nonpalpable prostate tumors in patients diagnosed using extensive transperineal ultrasound-guided template prostate biopsy. Cancer 2005;103(9):1826–1832.

Eisenberg ML et al: The importance of tumor palpability and transrectal ultrasonographic appearance in the contemporary clinical staging of prostate cancer. Urol Oncol 2011;29(2):171–176.

Huffman JL et al: Ureteral catheterization, retrograde ureteropyelography and self retaining ureteral stents. In: Bagley DH et al (eds): Urologic Endoscopy: A Manual and Atlas. Little, Brown and Company, Boston, Toronto, 1985, pp. 163–177.

Monga M: The dwell time of indwelling ureteral stents—the clock is ticking but when should we set the alarm? J Urol 2011;185(2):387.

Nash PA et al: Sono-urethrography in the evaluation of anterior urethral strictures. J Urol 1995;154:72.

Phan CN, Stoller ML: Helically ridged ureteral stent facilitates the passage of stone fragments in an experimental porcine model. Br J Urol 1993;72:17.

Stone Basketing

de la Rosette JJ et al: Handling and prevention of complications in stone basketing. Eur Urol 2006;50(5):991–998.

Dourmashkin RL: Cystoscopic treatment of stones in the ureter with special reference to large calculi: Based on a study of 1550 cases. J Urol 1945;54:245.

Leone NT et al: Changing trends in the use of ureteroscopic instruments from 1996 to 2008. J Endourol 2010;24(3):361–365.

Wang CJ et al: Randomized trial of NTrap for proximal ureteral stones. Urology 2011;77(3):553–557.

Wolf JS Jr et al: Cost-effectiveness vs. patient preference in the choice of treatment for distal ureteral calculi: A literature-based decision analysis. J Endourol 1995;9:243.

Cytology, Biopsy Histology

Dodd LG et al: Endoscopic brush cytology of the upper urinary tract: Evaluation of its efficacy and potential limitations in diagnosis. Acta Cytol 1997;41:377.

Endoscopy

Hopkins HH: The modern urological endoscope. In: Gow JG, Hopkins HH (eds): A Handbook of Urological Endoscopy. Churchill Livingstone, Edinburgh, London, New York, 1978, pp. 20–34.

Merkle EM et al: Virtual cystoscopy based on helical CT scan datasets: Perspectives and limitations. Br J Radiol 1998;71:262.

Reuter MA, Reuter HJ: The development of the cystoscope. J Urol 1998;159:638.

Lithotripsy

Bapat SS: Endoscopic removal of bladder stones in adults. Br J Urol 1977;49:527.

Hussein NS, Gohar MR: Pneumatic ureterolithotripsy in paediatric and adolescent patients: A ten-year experience at the Hospital Universiti Sains Malaysia. Singapore Med J 2011;52(1):42–46.

Kara C et al: Transurethral cystolithotripsy with holmium laser under local anesthesia in selected patients. Urology 2009;74(5):1000–1003.

Vassar GJ et al: Holmium:YAG lithotripsy efficiency varies with energy density. J Urol 1998;160:471.

This page intentionally left blank

Percutaneous Endourology and Ureterorenoscopy

9

David B. Bayne, MD, MPH; Joachim W. Thüroff, MD;
Rolf Gillitzer, MD; & Thomas Chi, MD

Endoscopic procedures in the kidney rely on two primary approaches: retrograde and antegrade instrumentation of the upper urinary tract. The retrograde approach utilizes ureterorenoscopy to traverse the urethra and ureter, while antegrade instrumentation requires a percutaneous puncture directly into the kidney. Both approaches must respect the intrarenal anatomy just as in open renal surgery, and imaging is required for safety.

PERCUTANEOUS RENAL ACCESS

To safely enable percutaneous renal access, the most important principle is to identify a puncture direction that will provide direct access to the target and safe, bloodless instrumentation. Visualization of both the puncture needle and the target and precise guidance of the needle tip to the target require imaging techniques such as ultrasound, fluoroscopy, and, in selected cases, computed tomography (CT).

Contraindications to percutaneous kidney puncture are blood-clotting anomalies due to coagulopathies or pharmacologic anticoagulation. Sterile preparation and draping of the surgical field are required in the same way as for open surgery, although these procedures are generally categorized as clean-contaminated and not sterile given entry into the genitourinary tract. Local anesthesia suffices only for puncture of the kidney and small-bore tract dilation (6–12Fr), for antegrade insertion of a ureteral stent or nephrostomy catheter. Lidocaine hydrochloride 2% USP, 10 mL, can be given for infiltration of the skin and tissues along the intended tract of puncture down to the renal capsule. For larger-bore tract dilation of ≤30Fr, general anesthetic is usually recommended for both patient comfort procedural accuracy, although local or regional anesthetic can be used when absolutely required.

IMAGING AND PUNCTURE TECHNIQUES

Percutaneous puncture of the renal collecting system may be performed for diagnostic procedures (eg, antegrade pyelography, pressure/perfusion studies) or to establish access for therapeutic interventions (Table 9–1).

Both ultrasonic scanning and fluoroscopy provide visualization and guidance for a safe, accurate percutaneous puncture, but ultrasound has the following definite advantages:

1. Shorter learning curve to master renal access compared to fluoroscopic guidance
2. Easier identification of posterior calyces for safe renal entry
3. No intravenous or retrograde administration of contrast dye
4. No radiation exposure
5. Continuous real-time control of puncture
6. Imaging of radiolucent, non-contrast-enhancing renal and extrarenal structures (eg, renal cyst, retroperitoneal tumor) for puncture
7. Imaging of perirenal structures that should be avoided during needle passage (eg, bowel, lung, liver, spleen)
8. Reduced cost relative to fluoroscopic guidance

Fluoroscopy may be easier to use in the nondilated collecting system or in the presence of staghorn stones compared to ultrasound. Once the puncture needle has entered the renal collecting system, both ultrasound or fluoroscopy can be used for control and guidance of subsequent steps (eg, guidewire insertion, tract dilation, catheter insertion). However, most dilation instruments are currently designed to be compatible with fluoroscopic visualization, and fluoroscopy facilitates clearer visualization of wire passage down the ureter.

For percutaneous puncture of the renal collecting system, a variety of patient positions can be utilized, including both the prone and modified supine positions. For prone puncture, radiolucent bolsters may be placed under the abdomen to correct for lumbar lordosis and to support the kidney. We teach the standard fluoroscopic lower pole prone puncture site to be two fingerbreadths lateral to the lateral border of the paraspinal muscle and two fingerbreadths inferior to the 12th rib; this skin entry site ensures that the access tract is

Table 9–1. Indications for percutaneous puncture of the renal collecting system.

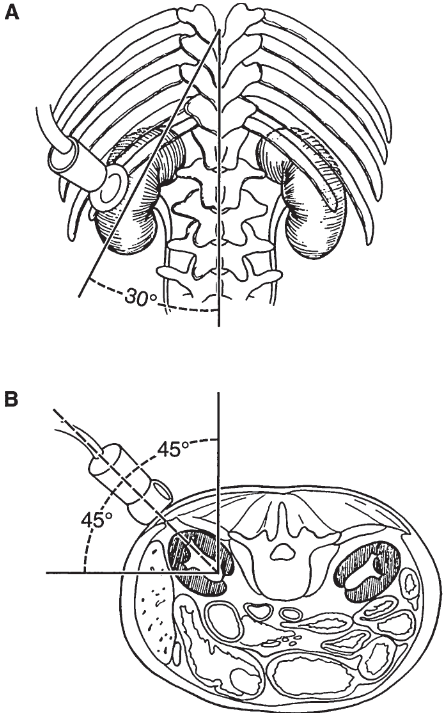
Diagnostic indications
Antegrade pyelography
Pressure/perfusion study (Whitaker test)
Therapeutic indications
Nephrostomy catheter drainage
Antegrade ureteral stenting
Dilation of ureteral strictures
Percutaneous endopyeloplasty
PNL
Percutaneous resection and coagulation of urothelial tumors

PNL, percutaneous nephrolithotomy.

likely to avoid traversing the bowel, and provides a comfortable working angle into the kidney for stone removal. In general, the more lateral and anterior the puncture side, the greater the concern for bowel injury. To image the kidney with ultrasonography, ultrasonic scanning is performed below the 12th rib to obtain a longitudinal scan of the kidney. To optimize coupling of the ultrasonic probe to the skin, sterile saline, water, or gel can be applied to the skin at the scanning site. In the frontal view of an intravenous pyelogram, the long axis of the kidney usually follows the psoas muscle, forming an approximately 30° angle with the midline (Figure 9–1A). In the transverse view of a CT scan, the transverse axis of the kidney forms a ~45° angle with both a horizontal line and a sagittal line (Figure 9–1B). The position and direction of the transducer should be oriented roughly to the following marks: below the 12th rib (if possible), cranial to the puncture site, with a 30° caudal–lateral rotation, and with a 45° lateral tilt of the scanning head. For supine percutaneous nephrolithotomy (PCNL), modified lithotomy positioning involves using bolsters to create slight flank elevation of the operative side. Similar to the prone approach, either fluoroscopy or ultrasound can be used to obtain proper visualization of the collecting system during needle access in the supine position.

Whether using ultrasound or fluoroscopy, factors that influence the choice of scanning technique and puncture site include patient size; position and rotation of the kidney; anomalies of bony structures; positions of the colon, spleen, liver, and lung relative to the kidney; and the target of puncture (upper, middle, or lower calyx; caliceal diverticulum). With ultrasound, the probe head can be positioned to provide the best visualization and optimum puncture site for each patient. Thus, a puncture site as high as above the 11th rib may be chosen if the lung is not visualized in the puncture direction. A different puncture site must be chosen if bowel gas or the liver or spleen is visualized within the intended puncture direction.

The puncture direction should always aim through a pyramid into a target calyx; puncture into an infundibulum may result in bleeding from segmental and interlobar vessels in the renal sinus, and direct puncture of the renal pelvis renders dilation of the nephrostomy tract and insertion of catheters and instruments difficult, with increased risk of accidental catheter displacement after collecting system entry. Calyceal selection should be based on the ability to optimally reach all stones intended for removal. In the prone position, this is most safely done in a posterior calyx, which allows collecting system entry without torquing of instruments across the renal infundibulum, thus preventing significant bleeding. Stones in caliceal diverticula are often approached by direct puncture of the diverticulum.

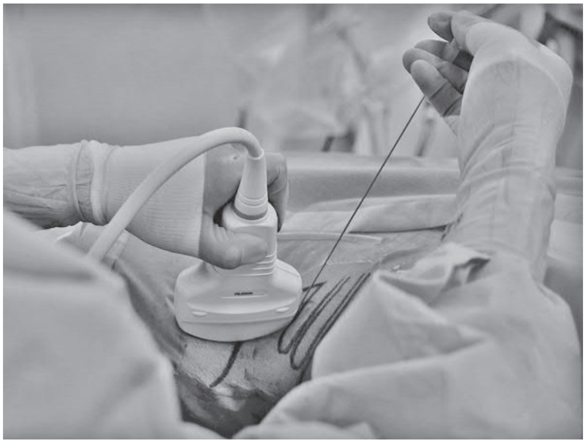


▲ **Figure 9–1.** Renal ultrasound. ***A:*** Long axis of kidney forms a 30 degree angle with midline. ***B:*** Transverse axis of kidney forms a 45 degree angles with horizontal and sagittal lines.

Once chosen, the target for access to the renal collecting system must be visualized either fluoroscopically or by ultrasonography. A 16–18-gauge puncture needle (Figure 9–2) may then be inserted under direct ultrasound or fluoroscopy imaging guidance.

UTRASOUND-GUIDED RENAL ACCESS

The ultrasound probe should be positioned in such a way that both the target and the puncture needle are visualized in the same scanning plane and the needle is aligned so that its tip can be clearly seen. Bouncing the needle makes the tip more

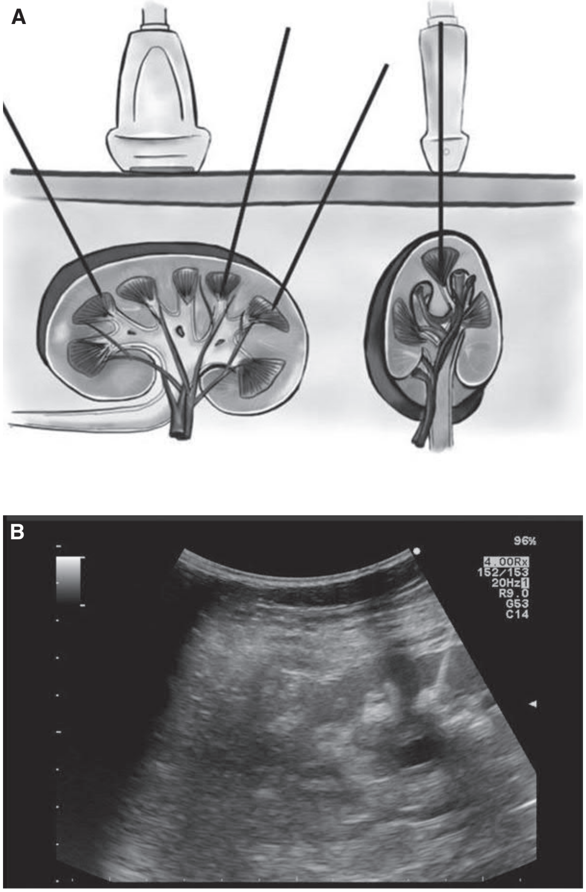


▲ **Figure 9–2.** Puncture needle inserted under ultrasound guidance.

visible while the position of the probe head is being adjusted. The needle can be safely moved back and forth down to the renal capsule as often as necessary, but the renal parenchyma ideally should be punctured only once.

A needle guide attached to the scanning head can be used to direct the needle within the ultrasonic scanning plane. With some needle guides, the angle of puncture relative to the longitudinal axis of the scanning plane (depth) is also fixed and projected on the monitor by an electronically generated line. If either a steeper or flatter angle of puncture is desired, the entire scanning head and attached needle guide must be tilted, and the choice of puncture site will therefore be limited. Another drawback of a needle guide is that it does not allow for independent adjustment of the puncture and scanning direction if the needle deviates from its intended direction after being advanced through the skin. This frequently occurs in patients with scars from previous operations and becomes more of a problem the farther the target is from the cutaneous puncture site. Freehand puncture with individual adjustment of puncture and scanning direction is preferable in these cases.

Movement of the kidney during respiration may complicate renal puncture if the target is small and is visible on the monitor only during a specific respiratory phase. If the direction of the needle and the position of the target are aligned and both are clearly seen on the monitor, the needle is advanced through the renal capsule during the appropriate phase of respiration (Figure 9–3). In this phase, the kidney is usually pushed to some extent by the puncture needle so that visualization of needle and target may be momentarily impaired. However, as soon as the tip of the needle has penetrated the fibrous renal capsule, it is seen even more clearly. If both the tip of the needle and the target are visualized clearly at the same spot on the scanning plane, the needle is in the desired space.



▲ **Figure 9–3.** ***A:*** Freehand needle puncture under ultrasound guidance in the longitudinal plane of the ultrasound probe. ***B:*** Ultrasound visualization of the needle after penetration of the renal capsule.

FLUOROSCOPY-GUIDED RENAL ACCESS

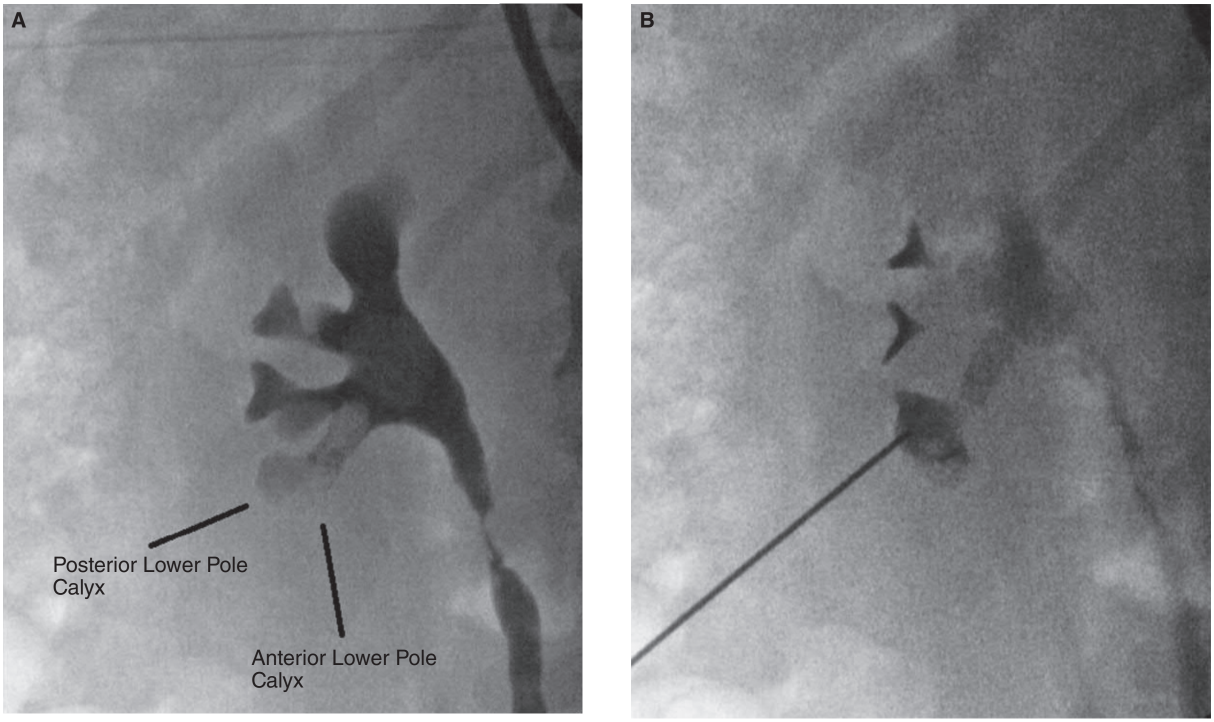
Antegrade injection of a small amount of contrast dye for fluoroscopy outlines the renal collecting system after successful puncture. However, if the collecting system has not been successfully punctured at the first attempt, contrast dye may fill the interlobar veins, which form a basket-like structure around the calyx, or the dye may extravasate. In rare cases in which contrast dye is injected into the adventitia of the renal collecting system, extravasation may assume the configuration of the collecting system, mimicking successful puncture. Care must be taken to inject the least amount of dye necessary so that further fluoroscopic and ultrasonic orientation will not be hindered. A greater amount of dye injected outside the collecting system may compress the calyx to be entered and render puncture more difficult. After opacification of the collection system is achieved, appropriate calyceal selection is tantamount. In the prone position, for the lower pole in most cases, the second calyceal target up from the bottom is the posterior calyx. In the upper pole, either the medial or lateral calyx can be chosen to provide adequate renal access. Access can be gained with either a triangulation or a bull's-eye technique.

If fluoroscopy is used for guiding renal puncture, either direct access with a 16–18-gauge needle or a fine-needle (20–22-gauge) puncture technique may be used. Intravenous or retrograde administration of contrast dye is needed. With retrograde injection, an open-ended or ureteral balloon occlusion catheter can be inserted to cause slight distention of the renal collecting system; this facilitates puncture of a nondilated system. For the fine-needle technique, first, a 16–18-gauge needle is inserted through the abdominal wall only, and a longer fine needle is inserted coaxially through the larger needle (Figure 9–4B). This technique improves control of the fine needle. As soon as the fine needle has entered the collecting system, the larger needle can be advanced over the fine needle, which serves as a guide. After withdrawal of the fine needle, a regular guidewire can be inserted through the large needle into the collecting system. Once the collecting system is entered (Figure 9–4A), fluoroscopy or ultrasound can be used to guide the subsequent steps of the procedure. Urine aspirated from the collecting system should be cultured, especially if there is suspicion of a urinary tract infection.

ANTEGRADE PYELOGRAPHY AND PRESSURE/PERFUSION STUDIES

Renal puncture is rarely indicated for diagnostic antegrade pyelography only, because less invasive radiographic techniques are available (eg, intravenous pyelography, ultrasound, CT, magnetic resonance imaging [MRI], retrograde pyelography). However, obtaining a radiograph after antegrade injection of contrast dye should be an integral part of every percutaneous puncture for any indication. Before contrast dye is injected, urine must be aspirated to decompress an obstructed collecting system. The contrast dye should be diluted to 20–30% for better visualization of details; antegrade pyelography then provides images of the collecting system with about the same resolution of detail as retrograde pyelography.

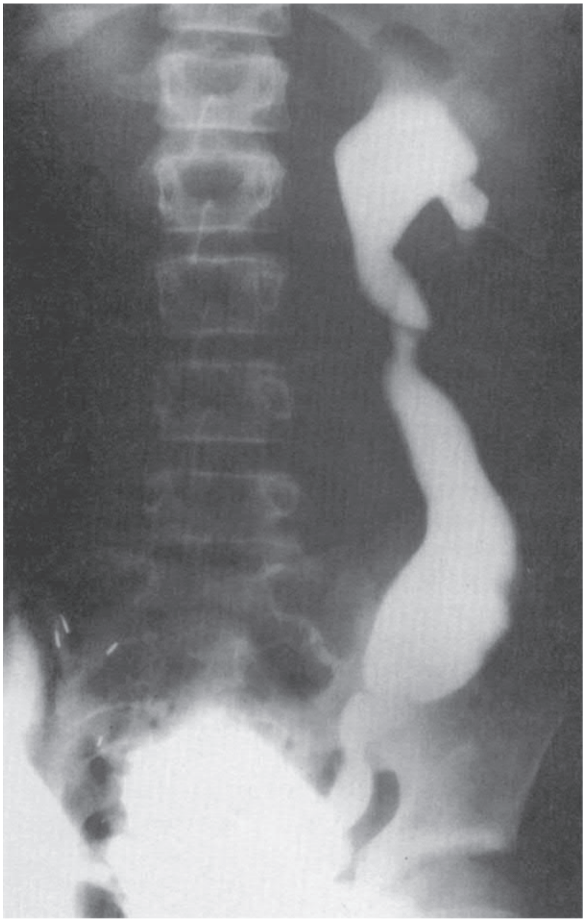
Antegrade pyelography is also performed in conjunction with a percutaneous pressure/perfusion study (Whitaker test) to assess pyeloureteral resistance. Percutaneous urodynamic



▲ **Figure 9–4.** ***A:*** Retrograde fluoroscopic image of collecting system with patient in prone position with anterior and posterior calyx of lower pole labeled. ***B:*** Fluoroscopic image showing percutaneous needle access of the posterior lower pole.

studies of the dilated upper urinary tract are indicated only in the 10–30% of cases in which noninvasive radioisotope studies (diuresis renogram) fail to differentiate an obstructed dilated system from an unobstructed dilated system. This is more likely in cases of ureterovesical obstruction than in pelvic–ureteral obstruction, in which diuresis renograms are reliable.

The Whitaker test provides simultaneous measurements of intrapelvic and intravesical pressures during antegrade perfusion, with flow rates of 5, 10, 15, and 20 mL/min. Puncture of the renal collecting system is performed with a coaxial needle–catheter system with an outer 6Fr catheter for the renal pressure–perfusion study; thus, puncture and catheter insertion can be done as a one-step procedure. Perfusion is started with flow rates of 5–10 mL/min until steady-state equilibrium of pressure readings is reached and the entire upper urinary tract is opacified (Figure 9–5). Pressure readings may be obtained intermittently from the perfusion catheter via a three-way stopcock, or continuously, if a double-lumen nephrostomy catheter or two separate catheters for perfusion and pressure measurement are used. Continuous recordings during perfusion from a single-lumen perfusion catheter via a T connection yield erroneous pressure readings (the smaller the lumen of the nephrostomy catheter and the higher the perfusion rate, the higher the pressure reading), unless the resistance of the entire system was previously calibrated for each rate of perfusion. To obtain accurate pressure readings, the positions of the intrapelvic and intravesical pressure manometers must be adjusted to the level of the renal pelvis and bladder, respectively. At a flow rate of 10 mL/min, differential pressures (renal pelvic pressure minus bladder pressure) below 13 cm water are normal, between 14 and 22 cm water suggest mild obstruction, and above 22 cm water suggest moderate to severe obstruction. At flow rates of 15 and 20 mL/min, upper limits of normal pressure are 18 and 21 cm water, respectively.

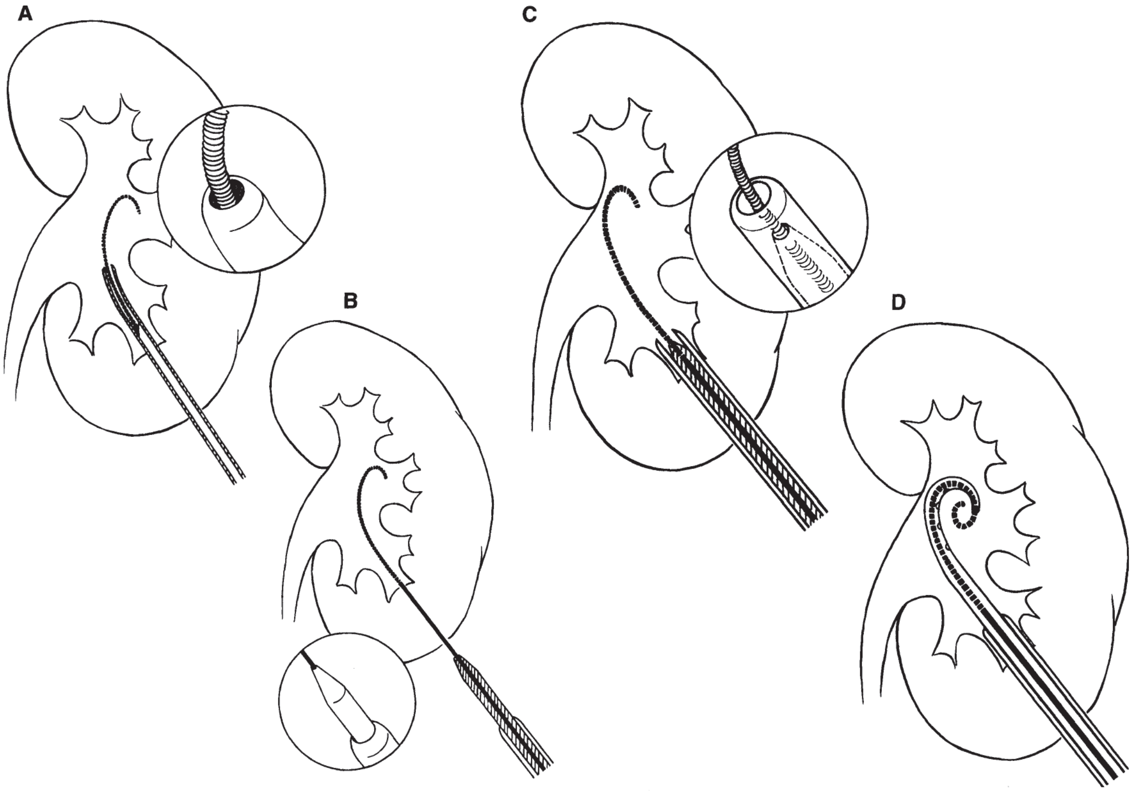


▲ **Figure 9–5.** Upper tract opacification during Whitaker test.

PERCUTANEOUS CATHETER PLACEMENT

Percutaneous nephrostomy catheter placement for drainage and decompression of the upper urinary tract is indicated if retrograde ureteral catheterization is not advisable (eg, in sepsis with hemodynamic instability too great to safely tolerate general anesthetic) or proves to be impossible (eg, impassable ureteral obstruction due to stone, tumor, or stricture). After percutaneous endourologic procedures, a nephrostomy catheter or internalized ureteral stent is usually left indwelling for at least 24 hours. To convert a nephrostomy catheter diversion into internal stent drainage, antegrade ureteral stenting through the nephrostomy tract may be attempted even in cases in which previous attempts at retrograde stenting have failed. The antegrade approach to stenting can be expected to be successful if failure of retrograde stenting was not related to mere mechanical ureteral obstruction but rather to ureteral tortuosity, false passage (ureterovaginal fistula, urinoma after open surgery), or inability to identify the orifice endoscopically (ureterointestinal anastomosis).

For diagnostic procedures such as pressure/perfusion studies (Whitaker test), a 6Fr catheter is sufficient. Catheters of this size can be placed in a one-step procedure of puncture if coaxial needle–catheter systems are used (Figure 9–2). For therapeutic interventions such as nephrostomy drainage or antegrade ureteral stenting, softer, larger catheters must be inserted, and puncture tract dilation is necessary before catheter insertion. For dilation of a puncture tract, a 0.035- or 0.038-in. guidewire must be inserted into the collecting system, either directly through the puncture needle or through the outer catheter of a coaxial needle–catheter system. Curved-tip (J) guidewires are less likely to cause damage to the mucosa of the renal pelvis than are straight guidewires. One of the most common problems of tract dilation is kinking of the guidewire during insertion of fascial dilators; therefore, guidewires with a floppy tip and a stiff proximal section (Lunderquist wire) are



▲ **Figure 9–6.** Small-bore tract dilation and nephrostomy catheter insertion. ***A:*** Insertion of guidewire into collecting system. ***B:*** Insertion of fascial dilator over guidewire. ***C:*** Insertion of introducer sheath system over guidewire. ***D:*** Insertion of nephrostomy catheter through access sheath.

preferable over floppy guidewires. If the tip of the guidewire cannot be advanced into the renal pelvis because it is trapped in a dilated calyx with a narrow infundibulum or because an obstructing stone hinders passage, the outer catheter of a coaxial needle–catheter system can be used to manipulate the guidewire into the collecting system (Figure 9–6A), or angiographic catheters with different curved-tip configurations may be inserted over the guidewire for this purpose. Once the guidewire is in the correct position (upper calyx, renal pelvis, upper ureter, down the ureter into the bladder), radiopaque fascial dilators can be inserted under imaging guidance with rotating movement of the dilator during advancement. If flexible plastic fascial dilators are used, sequential insertion of dilators of increasing size (usually in 2Fr steps) is necessary. If stiff metal or Kevlar dilators are used, dilation from 6Fr to 10–12Fr is possible in a one-step procedure.

After tract dilation, relatively stiff nephrostomy catheters (eg, polyethylene catheters) can be introduced easily over the guidewire. However, if softer catheters (eg, silicone or polyurethane catheters) are to be inserted, use of an introducer sheath is helpful. An introducer sheath is also helpful for antegrade ureteral stenting and for insertion of nephrostomy catheters with various self-retaining configurations of the tip (eg, pigtail). These catheters can be stretched into a straight configuration while being inserted through the introducer sheath and over a guidewire; the tip resumes its original configuration, due to the memory function of the material once the guidewire is withdrawn. The introducer sheath can be inserted with the last fascial dilator in a one-step procedure if a coaxial dilator–introducer sheath system is used (Figure 9–6B, C). The use of an introducer sheath provides universal access to the renal collecting system for placement of all types of catheters (nephrostomy catheters [Figure 9–6D], ureteral stents, balloon dilation catheters) and safety and working wires for different systems of large-bore nephrostomy tract dilation required for insertion of endoscopic instruments.

Nephrostomy catheters should be soft to avoid discomfort and irritation of the renal pelvis and should have a self-retaining mechanism or should be placed with enough slack to prevent dislodgement from the collecting system during movement of the kidney. Standard nephrostomy catheters are

Malecot catheters, pigtail catheters, and loop catheters. Loop catheters have a very effective retaining mechanism; they may cause serious complications, however, if the catheter is accidentally pulled out of the kidney.

Antegrade ureteral stenting can be done through the introducer sheath using either open- or closed-tip stents. Catheters with open-tip configuration are advanced with a pusher catheter over a guidewire, which must be inserted through the introducer sheath down the ureter and into the bladder as a first step. Catheters with closed-tip configuration are advanced by pushing the indwelling wire. In either technique, a thread through the proximal side hole of the catheter ensures that the catheter can be pulled back into the renal pelvis if it is advanced too far. The thread must be pulled out before the guidewire is withdrawn so that the pusher catheter can still hold the double-J stent in place.

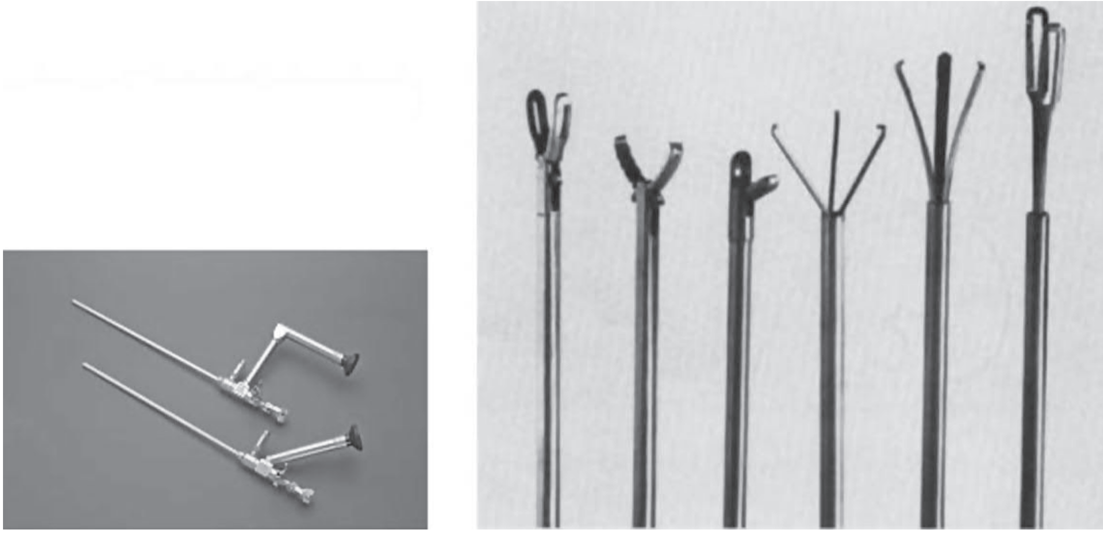
An introducer sheath may also be used for insertion of a 7Fr balloon dilation catheter over a guidewire into the ureter to dilate ureteral strictures to 12–18Fr with balloon pressures of ≤15 atm. After successful dilation, an 8–10Fr stent is usually left indwelling for several weeks. This technique is most successful in ureteral strictures that are a complication of recent surgery for benign disorders, except ureteropelvic obstruction. Longstanding strictures or strictures due to tumor compression of the ureter, radiation damage, or ischemic ureteral necrosis after radical pelvic surgery are not likely to respond favorably to balloon dilation.

ENDOSCOPIC INTRARENAL INSTRUMENTATION

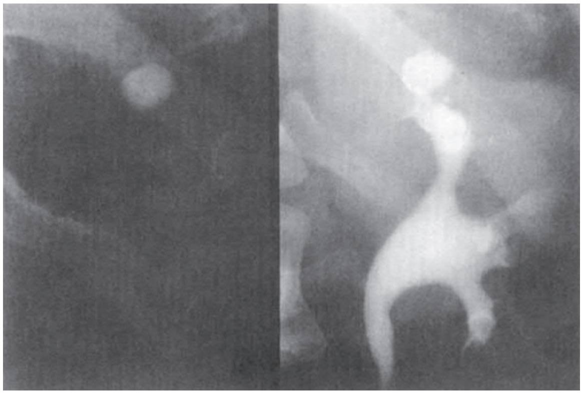
Nephroscopes are endoscopic instruments with sheaths of 15–26Fr that are inserted percutaneously through a nephrostomy tract. Standard rigid instruments are available in sizes of 18–26Fr; these have telescopes with offset eyepieces (Figure 9–7, left). Rigid instruments such as graspers and ultrasound probes can be inserted through a central working channel (Figure 9–7, right). Flexible fiberoptic nephroscopes may be used as well. These have a deflecting mechanism for the tip that allows inspection of otherwise difficult-to-reach calyces. A smaller working channel allows insertion of flexible instruments such as stone baskets, wire graspers, and electrohydraulic or laser probes. However, instrumentation through flexible nephroscopes is limited by the size and flexibility of working instruments such as stone forceps, and flexible endoscopes do not offer the optical quality and durability of rigid nephroscopes.

Nephroscopy is rarely indicated for diagnostic purposes only; in most cases, it is performed for percutaneous lithotripsy and extraction of renal stones (PCNL) or resection of tumor. PCNL is still indicated in cases for which shockwave lithotripsy (SWL) or ureteroscopy is not the primary choice of treatment. Such cases include urinary obstruction not caused by the stone itself, large-volume stones, and stones that cannot be accessed easily with ureteroscopy. PCNL can achieve stone-free rates of >90%. Nephroscopes also may be used for direct-vision internal incision of ureteropelvic stenosis and for endoscopic treatment of urothelial tumors of the upper urinary tract.

Insertion of a nephroscope into the renal collecting system requires dilation of the puncture tract. With modern scopes, the size of the dilation tract can be as small as 8Fr or as large as 30Fr. A safety wire should be inserted parallel to the working wire and advanced into an upper calyx or the upper ureter to guide the way back into the collecting system in case the dilator and working wire become displaced accidentally. Insertion of an introducer sheath during small-bore



▲ **Figure 9–7.** ***Left:*** Nephroscopy telescopes. ***Right:*** Percutaneous access working channels with grasping instruments.



▲ **Figure 9–8.** ***Left:*** X-ray image of stone in caliceal diverticulum. ***Right:*** Opacification of collecting system showing caliceal diverticulum as an offshoot of upper pole calyx.

tract dilation to 10–12Fr facilitates parallel insertion of safety and working wires. The central metal catheter of a coaxial metal dilator system, the central plastic catheter for insertion of sequential plastic dilators, or a balloon dilator can be inserted over the working wire. Balloon dilators of 9Fr size can dilate a nephrostomy tract to a diameter of ≤30Fr under pressure of ≤30 atm in a one-step procedure. This may prove difficult or impossible if perirenal scar tissue from previous surgery prevents complete expansion of the balloon over its entire length. Sequential plastic dilators allow stepwise dilation of the tract under fluoroscopic control; however, on withdrawal for insertion of the next-larger dilator, compression of the tract is lost intermittently and bleeding occurs into the collecting system, sometimes hindering subsequent endoscopy. Reusable Alken coaxial metal dilators (Figure 9–8, right) (each dilator slides over the next-smaller one) allow stepwise tract dilation even in the presence of severe scarring with continuous nephrostomy tract compression for improved hemostasis.

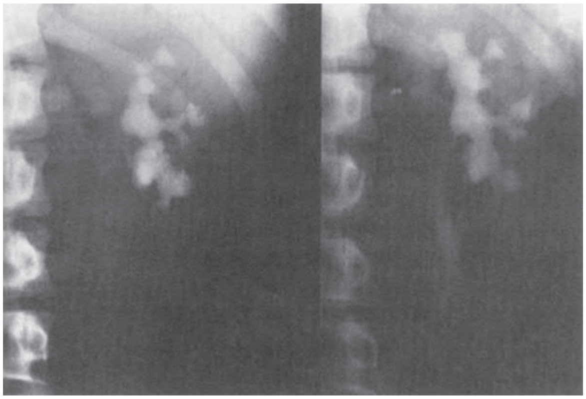
With any dilation technique, the last step is insertion of a working sheath, which can be either the metal working sheath of the nephroscope or a larger disposable sheath. With the balloon dilation technique, the working sheath must be introduced over the balloon dilator; with use of serial plastic or coaxial metal dilators, the working sheath slides over the last dilator. Larger sheaths provide better drainage of irrigation fluid with lower intrapelvic pressures but may be associated with higher bleeding risk. Selection of tract dilation size is a reflection of stone volume and complexity as well as patient characteristics.

▶ Renal Stones

In the era of SWL and ureteroscopy, indications for PCNL generally include the following:

1. Urinary obstruction not caused by the stone itself (eg, stone in a caliceal diverticulum [Figure 9–8, left and right], stone in association with ureteropelvic stenosis) where the stone is inaccessible via ureteroscopic means. These stones could be broken up by SWL or ureteroscopy, but gravel would not pass spontaneously.
2. Large-volume stones (>2 cm) (Figure 9–9, left and right) (eg, staghorn stones). These stones can be treated by several sessions of ureteroscopy, but patients are faced with multiple procedures and lower stone-free rates. Shockwave lithotripsy is generally not a good choice for these large stone burdens.
3. Stones that cannot be positioned within the focus of the shockwave apparatus in patients for whom ureteroscopy is not a viable option (eg, patients with stones in kidneys with abnormal position due to anomalies of the urinary tract or skeleton, stones in transplanted kidneys, kidney stones in very obese patients that cannot be positioned into the focus of the shockwave source because of the increased distance from skin to stone, or when the weight limit of the SWL table is exceeded).
4. Lower pole caliceal calculi in the 1–2-cm range. The overall stone-free rate for these stones with either SWL or ureteroscopy is only as high as 60%.

Large-volume staghorn stones are a common indication for PCNL. Small stones can be extracted with a variety of rigid forceps and graspers (Figure 9–7, right). Stones may be retrieved from difficult-to-reach calyces with flexible wire baskets and graspers inserted through flexible nephroscopes. Large stones must be disintegrated using mechanical, pneumatic, ultrasonic, electrohydraulic, or laser energy. Hollow ultrasonic probes allow for controllable, systematic stone disintegration under continuous suction for removal of sand and smaller fragments. Electrohydraulic probes are more powerful than ultrasonic probes and may be used through



▲ **Figure 9–9.** ***Left:*** X-ray image showing staghorn stone. ***Right:*** same image with opacification of collecting system.

flexible nephroscopes, but they do not provide continuous suction and are associated with a higher risk of scattering stone fragments into inaccessible calyces and of damaging the mucosa of the renal pelvis. However, with electrohydraulic probes and the holmium:YAG laser, disintegration of hard or large stones is faster.

For soft stones, continuous disintegration and evacuation of fragments with ultrasound probes is most time-efficient. Hard stones should be broken up into the largest possible fragments that can be extracted through the working sheath. The ureteropelvic portion of a staghorn stone should be left in place until the procedure is nearly completed, as it will act like a plug in a drain to prevent the loss of fragments into the ureter. An antegradely or retrogradely positioned ureteral balloon occlusion catheter might serve the same purpose; however, the extra procedure of retrograde ureteral catheterization is rarely indicated.

Normal saline should generally be used as the irrigation fluid. Even with the low-pressure system provided by a large plastic working sheath, considerable amounts of irrigation fluid may be absorbed if small veins are opened and intrarenal manipulation is prolonged. This may cause electrolyte abnormalities similar to those seen in transurethral resection (TUR) syndrome with use of hypotonic fluids. Intraoperative administration of diuretics (eg, mannitol, 12.5 g) can be used to reduce intraoperative renal bleeding and also has proved effective in preventing intrarenal reflux. On completion of the procedure, a nephrostomy catheter or internalized ureteral stent is most often placed to maximally drain the kidney, although totally tubeless procedures can be performed in the appropriately selected patient.

Nephrostomy catheters may be removed as soon as the day after stone removal surgery. Often antegrade pyelography is used to check for unobstructed upper urinary tract drainage prior to tube removal. Injection of methylene blue into the tube and searching for its presence in the bladder or a nephrostomy tube capping trial are alternative methods of determining ureteral patency prior to tube removal. In cases of postoperative profuse hemorrhage, the nephrostomy catheter can be occluded for 1–2 days to allow for tamponade formation. Blood clots usually dissolve later spontaneously as a result of urokinase activity without problems. After removal of a large-bore nephrostomy catheter (22–24Fr), urinary discharge from the nephrostomy tract can persist for several days and be bothersome to the patient. This usually resolves spontaneously after 2–3 days provided antegrade ureteral patency is present.

Some experienced endourologists have propagated percutaneous stone treatment and endopyelotomy without standard placement of a nephrostomy catheter. Major advantages are marked reduction in analgesia requirements and length of hospitalization. While no objective prerequisites have been clearly delineated, some factors associated with successful tubeless (no nephrostomy tube, but the presence of a ureteral stent) and totally tubeless PCNL procedures are a small to moderate stone burden and no residual fragments, not more than two percutaneous tracts in one session, and no significant bleeding. Bleeding arising from the nephrostomy tract can be stopped nephroscopically by punctual electrocoagulation during withdrawal of the working sheath. For "tubeless" percutaneous renal surgery, expected patient discomfort from the nephrostomy catheter is traded against possible discomfort from the double-J ureteral stent and from cystoscopy to remove the stent later.

Ureteropelvic Stenosis

With the advent of PCNL and ureterorenoscopy, other endosurgical techniques have been developed that are similar to procedures used in the lower urinary tract. Direct-vision internal incision of ureteropelvic stenosis (pyelolysis, endopyelotomy, endopyeloplasty) seems to be a natural outgrowth of endoscopic techniques in the upper urinary tract. Compared with the retrograde techniques of endopyelotomy (incision with a cold knife, Acucise catheter, Greenwald electrode, or laser) and endoballoon dilation, the antegrade technique offers the advantage of an incision under direct vision. The cold-knife incision must be extended into the perirenal fat and is stented for 4–6 weeks to allow for healing, according to the principle of Davis' intubated ureterotomy.

Success rates of antegrade endopyelotomy of ≤65–95% are reported for primary cases and ≤89% for secondary cases after failed open surgical pyeloplasty.

The success rates for retrograde endopyelotomy with fewer patients and less follow-up than in antegrade endopyelotomy range between 73% and 90%; for the Acucise endopyelotomy, between 76% and 81% (see section on ureteropelvic stenosis). The candidates for best endoscopic (antegrade and retrograde) outcomes are those with less than grade II hydronephrosis and good renal function.

In most reports on endopyelotomy, the criteria of success differ from those of open pyeloplasty; relief of subjective symptoms is given priority over results of imaging studies such as decompression of a dilated collecting system on intravenous pyelography or renal ultrasound. Inadequate results after endopyelotomy may be related to a crossing vessel or to redundancy of the renal pelvis, which would be resected during open pyeloplasty. According to the law of Laplace, wall tension of a renal pelvis is, at the same intrapelvic pressures, higher in a more dilated collecting system with a larger diameter than in a less dilated system with a smaller diameter. A rise in tension supposedly represents a more important pathogenetic factor for developing progressive dilatation than elevated intrapelvic pressures due to anatomic obstruction of outflow. Secondary open pyeloplasty after failed endopyelotomy may be a more tedious operation with less satisfactory results in cases with extensive periureteral scarring, due to extravasation of urine after endopyelotomy than primary open pyeloplasty.

Renal Pelvis Tumor

Another technique of endoscopic surgery in the upper urinary tract is use of electroresection, electrocoagulation, electrovaporization, and neodymium:YAG laser coagulation for treatment of urothelial tumors of the renal pelvis. However, with the limited reports of treatment of upper urinary tract urothelial cancer endoscopically, recurrence rates are yet to be compared with those of standard surgical treatment.

Ensuring a strict follow-up, percutaneous management of transitional cell carcinoma of the collecting system may be an alternative to nephroureterectomy for patients with low-grade/low-stage tumors and for palliative treatment.

PERCUTANEOUS ASPIRATION AND BIOPSY

Percutaneous puncture of cystic or solid lesions of the kidney and the adjacent retroperitoneum is usually performed for diagnostic purposes, in some cases in combination with therapeutic intentions such as drainage of fluid collections or obliteration of renal cysts (Tables 9–2 and 9–3). Because most of these lesions are radiolucent and are not enhanced with intravenously administered contrast dye, they cannot be visualized by fluoroscopy. Thus, ultrasound or CT scans are the imaging techniques of choice to depict these lesions and guide percutaneous puncture. The technique of ultrasonically guided puncture is the same regardless of whether the target is the renal collecting system or a cystic or solid renal or extrarenal lesion. For cytologic aspiration, a fine-needle (20–22-gauge) aspiration technique is used that is comparable with fine-needle aspiration biopsy of the prostate. There is no evidence that one type of needle is preferable to the others. For aspiration and evacuation of renal cysts or extrarenal fluid collections (urinoma, lymphocele), the same coaxial needle/catheter system can be used as for percutaneous puncture of the renal collecting system. A small catheter (6–10Fr) is placed for a few days to ensure complete drainage of fluid. When fluids of high viscosity (abscess, hematoma) are to be drained, large-bore catheters (14–20Fr) must be inserted, necessitating dilation of the percutaneous tract. Percutaneous renal biopsy for histologic diagnosis and classification of renal disease is performed with 14–16-gauge needles (eg, Franklin–Silverman, Tru-Cut) at the lower pole of the kidney.

Table 9–2. Indications for puncture of renal and retroperitoneal lesions.

- Diagnostic indications
  - Fluid aspiration
    - Fluid chemistry
    - Bacteriology and sensitivity
    - Cytology
  - Radiography with percutaneously injected contrast dye
  - Histology (core biopsy)
- Therapeutic indications
  - Catheter drainage
    - Urinoma, lymphocele
    - Abscess, hematoma
  - Fluid evacuation and injection of sclerosing agent
    - Simple renal cyst

Table 9–3. Differential diagnosis of renal and retroperitoneal lesions.

- Renal cystic lesion
  - Benign cyst
  - Hydrocalix
  - Abscess
  - Hematoma
  - Cystic tumor
  - Tumor in cyst
- Retroperitoneal fluid collection
  - Urinoma
  - Lymphocele
  - Hematoma
  - Abscess
  - Cystic tumor
- Solid renal and retroperitoneal lesions
  - Benign tumor
  - Malignant primary tumor
  - Metastatic tumor

Renal Cysts

Renal cysts are found in about 50% of autopsy specimens in persons older than 50 years and are a frequent accidental finding on ultrasound or CT studies. With contemporary imaging techniques, diagnostic percutaneous puncture is rarely indicated. Percutaneous biopsy of cystic lesions is performed, but it rarely can be associated with spreading of malignant cells. Puncture for therapeutic procedures (evacuation of fluid and instillation of a sclerosing agent) is indicated if, because of its size or location, the cyst causes compression and urinary obstruction of the neck of a calyx or the ureter, or discomfort and pain.

Various tests may be performed on aspirated fluid. No one test is pathognomonic except cytologic findings of malignant cells. However, neoplasms within a benign-appearing cyst are exceedingly rare, and cystic degeneration of a renal neoplasm can usually be easily identified by ultrasound and CT. Benign cysts contain clear, straw-colored fluid with low fat and protein content and lactic acid dehydrogenase levels of <250 mIU/mL. Cancer is suspected if the fluid is bloody or murky and has a high content of fat, protein, and lactic acid dehydrogenase.

For therapeutic obliteration of cysts, sclerosing agents such as Pantopaque or 95% ethanol can be injected after complete evacuation of the cystic fluid. A volume of 10–100 mL of 95% ethanol, approximating 10–20% of the original volume of cystic fluid, is injected into the cyst and should be drained after 30 minutes. Percutaneous drainage and sclerosis of renal cysts is associated with a relatively high recurrence rate.

Retroperitoneal Fluid Collections

Low-viscosity retroperitoneal fluid collections (urinoma, lymphocele) are usually a complication of surgical procedures. However, urinoma may also be caused by exogenous trauma or by fornix rupture as a result of acute ureteral obstruction. Percutaneous techniques of catheter drainage eliminate the need for open surgical revision in most cases.

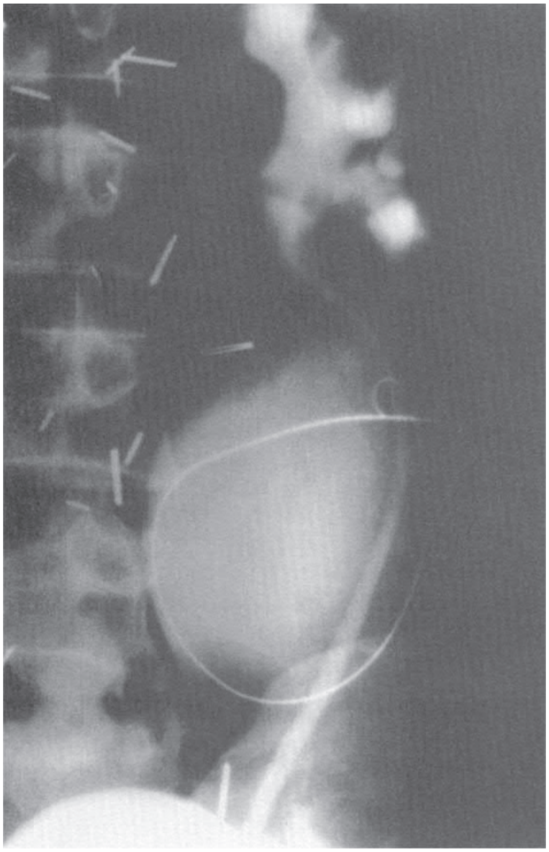
Insertion of a small (8–10Fr) catheter (with numerous side holes) is usually sufficient. Adjuvant measures are required to allow for sealing of a fluid leak or obliteration of a cyst. In cases of urinoma, the upper urinary tract must also be drained by a ureteral catheter or percutaneous nephrostomy catheter until drainage from the urinoma stops. Lymphoceles that develop following pelvic or retroperitoneal lymphadenectomy or renal transplantation often undergo spontaneous regression and seldom require puncture and drainage. However, large lymphoceles developing after retroperitoneal lymphadenectomy may cause pain and even ureteral obstruction (Figure 9–10). Patients should be treated with parenteral nutrition, systemic administration of somatostatin, and abdominal compression by bandaging, but if lymph drainage after percutaneous puncture and catheter placement persists for >1 week, surgical intervention with intraperitoneal marsupialization of the lymphocele and ligation or electrocoagulation of lymphatic vessels is indicated.

High-viscosity fluid collections (hematoma, abscess) usually require a large-bore (14–20Fr) percutaneous catheter for sufficient drainage. Perirenal hematomas are most frequently caused by surgical or exogenous trauma and rarely develop spontaneously in the presence of a bleeding disorder or following rupture of a renal tumor. Indications for percutaneous drainage are rare, as most small hematomas resolve spontaneously and should be followed by ultrasound or CT only. A hematoma that increases in size requires surgical intervention rather than percutaneous drainage. Secondary infection of a hematoma may be an indication for percutaneous drainage.

A perirenal abscess is mostly a complication of surgery or urinary stone disease; hematogenic renal abscess (renal carbuncle) is less frequent. Indications for puncture and drainage should be based on CT finding of a unifocal process that can be effectively and safely drained percutaneously. Multifocal renal abscess formation is often not amenable to percutaneous drainage.

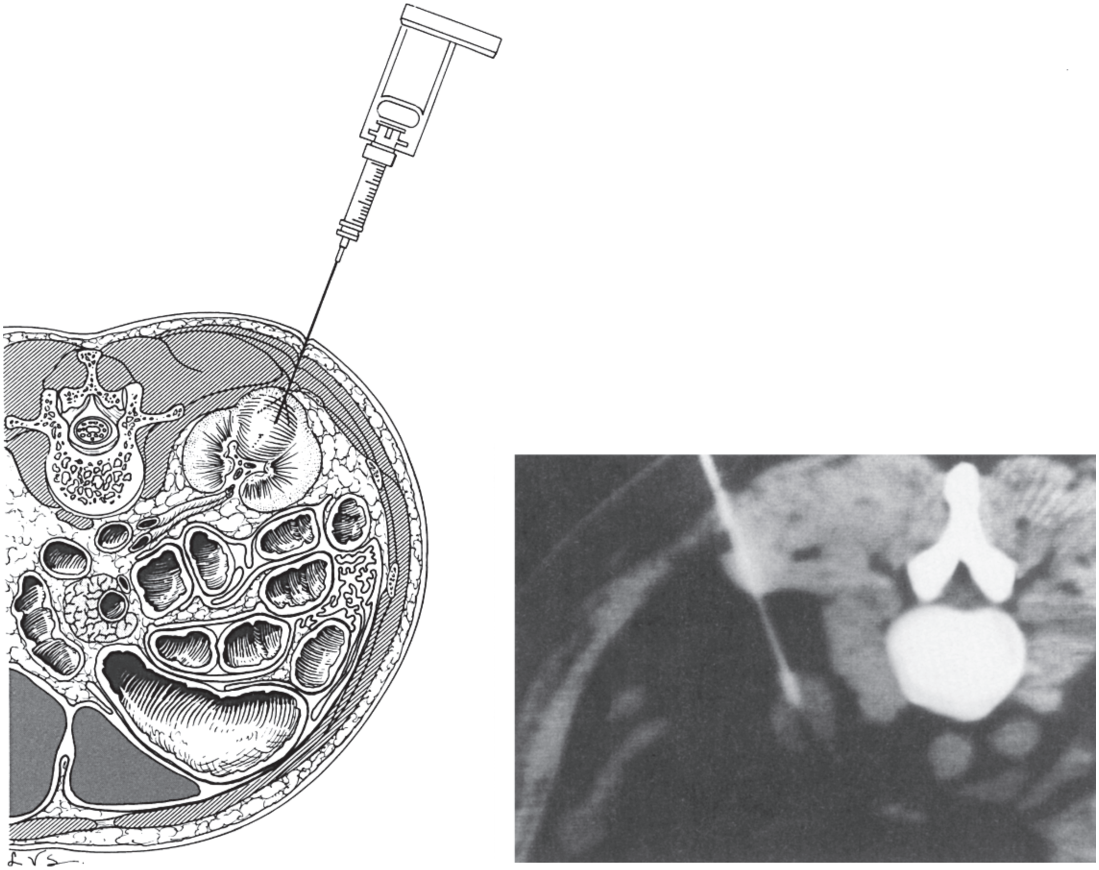
Renal and Retroperitoneal Tumors

Percutaneous aspiration biopsy of renal and retroperitoneal tumors is indicated if less invasive radiographic studies are inconclusive and if cytologic findings may have an impact on further medical or surgical therapy (Figure 9–11). If curative treatment by open surgery seems to be feasible, aspiration biopsy is rarely indicated. If the identity of a renal lesion is questionable or if conservative, organ-sparing surgery is technically feasible, surgical excision of the lesion with intraoperative frozen sections is preferable over percutaneous aspiration biopsy. However, aspiration biopsy may be indicated to avoid radical nephrectomy of a possibly benign lesion. In multifocal or possibly metastatic lesions, cytologic evaluation can be crucial for planning surgical or medical therapy, and in these cases, aspiration biopsy is usually indicated. Interpretation of cytologic findings is associated with a 10–25% incidence of false-negative findings and usually results from difficulty in discriminating normal renal tubular cells from low-grade renal cell cancer. As a rare complication, tumor seeding in the puncture tract has been described. The aspirate is immediately spread on glass slides. For standard Papanicolaou stains, alcohol fixation must be used.



▲ **Figure 9–10.** X-ray image showing lateralization of the ureter due to retroperitoneal collection.

Renal biopsy for diagnosis and classification of medical renal disease can be performed percutaneously or by open



▲ **Figure 9–11.** Percutaneous biopsy of renal mass.

surgery. Because specimens, rather than aspirates, are needed for diagnostic histologic study, large-bore (14–16-gauge) Franklin–Silverman or Tru-Cut needles are used. Ultrasonic or fluoroscopic guidance is preferable to blind renal puncture. However, even with puncture aimed precisely at the dorsal aspect of the lower pole of the kidney, where accidental injury to large vessels is less likely, bleeding is to be expected because of the vascularity of the parenchyma and is the major complication of this procedure (in approximately 5% of cases, with a mortality rate of 0.1%). Hematoma can usually be followed conservatively by ultrasound or CT scan, but transvascular embolization, open surgical revision, and even nephrectomy have been required following diagnostic renal biopsy. Open or laparoscopic surgical biopsy rather than percutaneous biopsy may be considered in patients with solitary kidneys or uncontrolled hypertension.

The widespread use of ultrasound has led to an increased rate of incidental diagnosis of small renal tumors, which account for 48–66% of renal cell carcinoma diagnoses. With the advent of minimally invasive techniques and improved radiodiagnostic possibilities, nonresectional renal tumor ablation is proving to be a viable strategy for the treatment of small renal masses based on short-term and intermediate-term oncological outcomes. The therapeutic strategies of local energy application aim at selective tumor destruction with minimal injury to the surrounding normal kidney parenchyma and reduced morbidity. Cryotherapy is the most widely evaluated probe ablative method for the treatment of small renal masses. The biological principle of cryotherapy is tissue destruction by repeated rapid freeze–thaw cycles down to temperatures below −20°C. Liquid argon and liquid nitrogen are the two most commonly used freezing agents. The cell destruction mechanism comprises intra- and extracellular ice crystal formation leading to intracellular dehydration and ultimately cell disruption. This is followed by a delayed cell death, which occurs during the thaw phase owing to vasoconstriction and microcirculatory failure. Repeating the freeze–thaw cycle intensifies tissue damage. However, since the freezing effect decreases with increasing distance from the freezing probe, the "iceball" must extend approximately 1 cm beyond the tumor margin to ensure complete tumor destruction. Radiofrequency ablation (RFA) involves coagulation of tumors by directly applying temperatures of 50–100°C throughout the tumor via needle electrodes. Since tissue carbonization at the electrode tip increases the impedance for radiofrequency transmission, tissue conductivity can be maintained by simultaneously irrigating saline through the tissue (“wet” RFA), resulting in larger RFA lesions for therapy of larger renal tumors. This can also be accomplished by multiple electrodes, which create overlapping ablation fields. The vicinity of larger-caliber vessels results in dissipation of heat (“heatsink effect”) and influences the efficacy of RFA negatively. Thus, peripheral exophytic tumors seem to be controlled better than central tumors in the vicinity of larger vessels.

Indications are similar for both techniques and are presently restricted to patients with comorbidity and/or advanced age who are not suitable candidates for surgical treatment, and in patients with impaired renal function, multiple bilateral tumors as in von Hippel–Lindau disease, and renal tumors in a solitary kidney. Guidelines for cryotherapy do not recommend treatment of tumors measuring >3 cm in size and for RFA, for tumors not >5 cm in size. Further relative contraindications for both procedures include hilar or central tumors and cystic tumors. An absolute contraindication is untreated coagulopathy.

The tumor mass can be approached by open surgery, laparoscopy, or percutaneously using fine probes and high-resolution imaging techniques. However, the minimally invasive character of the procedure itself ideally deserves a less invasive approach than open surgery. Proponents of laparoscopy emphasize the advantage of mobilizing the tumor and providing excellent exposure, thus avoiding damage to adjacent structures. It also allows for precise confirmation of probe positioning and monitoring the progress of the procedure such as development of the iceball in cryotherapy under direct vision. Percutaneous management requires MRI, CT scan with technical capabilities to construct three-dimensional pictures, or real-time ultrasound guidance for monitoring probe placement and progress of therapy. The percutaneous approach may be performed as an outpatient procedure, and it is typically reserved for posterior tumors. Special patients requiring multiple procedures as in von Hippel–Lindau disease thus may benefit from a percutaneous treatment. In contrast to cryoablation, which has the advantage of intraoperative laparoscopic and sonographic monitoring of the iceball, RFA lacks reliable real-time monitoring of the therapeutic progress. However, the introduction of real-time MRI guidance and monitoring of RFA may overcome this difficulty.

Both methods, cryotherapy and RFA, have shown promising results in carefully selected patients. Cryotherapy is associated with 93% and 81% 5- and 10-year cancer-specific survival, respectively. However, significantly increased local progression rates were calculated for cryoablation (relative risk = 7.45) and RFA (relative risk = 18.23) as compared with partial nephrectomy. Follow-up of partial nephrectomy series is still considerably longer than for ablative techniques. It must be emphasized that a significant selection bias exists in the application of these techniques. Published series of ablative treatment options include statistically significant older patients and smaller tumors as compared with the standard of partial nephrectomy. Also, a significant number of tumors treated with ablative techniques have unknown or indeterminate histology that could influence oncological results as a confounding factor. Furthermore, it is important to consider that different criteria may be used to define disease recurrence for ablative and for resectional techniques, hampering comparison of results. In contrast to cryotherapy, where tumor size decreases with time, tumor size after RFA remains mostly constant. Tumor size after successful cryotherapy can decrease up to 75% over 3 years, and tumors may even completely disappear on MRI in some cases. This fact is important for posttreatment surveillance. A major drawback of ablative techniques is the lack of reliable histologic confirmation of complete tumor ablation. Assessment is commonly done by CT scan. After RFA, a successfully ablated lesion becomes fibrotic and nonperfused and does not show contrast enhancement as compared with a viable tumor.

Major and minor complication rates of cryotherapy are 1.4% and 12.2%, and major and minor complication rates of RFA are 2.2% and 6%, respectively. The most commonly observed complications of cryotherapy and RFA are pain, paresthesia, and hemorrhage at the probe insertion site, occurring in approximately 5% of all patients. Rare complications include perinephric hematoma, renal rupture, UPJ obstruction, and damage to adjacent organs. Anteriorly or centrally located tumors that abut the UPJ pose an increased risk for complications, especially colonic injuries or lesions of the renal collecting system and ureter. Bleeding complications have decreased with the use of ultrathin probes (1.5 mm diameter). Specifically for RFA, bleeding can be minimized by active coagulation of the puncture tract while removing the probe. Conversion rates for cryoablation (3.5%) are similar to laparoscopic partial nephrectomy rates (3.9%) and higher than RFA rates (1.6%).

Ablative methods are still constantly evolving. Uncertainties exist regarding the exact amount of energy required, duration of treatment, mode of energy delivery, and types of electrodes used and render comparison of published results difficult. The adjunctive use of chemotherapeutic agents such as cyclophosphamide, 5-fluorouracil, and bleomycin or radiotherapy may have a synergistic effect on cryoablation and intensify its ablative capabilities. Further development of imaging techniques and combination with new technologies, such as single-port laparoscopic and natural orifice transluminal endoscopic surgery (NOTES), may potentially expand the indication range for ablative surgery. Cryotherapy may have equivalent efficacy for renal tumors measuring less than 4 cm. Long-term outcomes after cryoablation have proved to be inferior to resectional treatment in terms of local cancer

Table 9–4. Indications for ureterorenoscopy.

- Diagnostic indications
  - Lesions of ureter or renal pelvis
  - Hematuria from the upper tract
- Therapeutic indications
  - Ureteral stone treatment
  - Direct vision internal ureterotomy of ureteral strictures
  - Endoscopic resection and coagulation of ureteral tumors

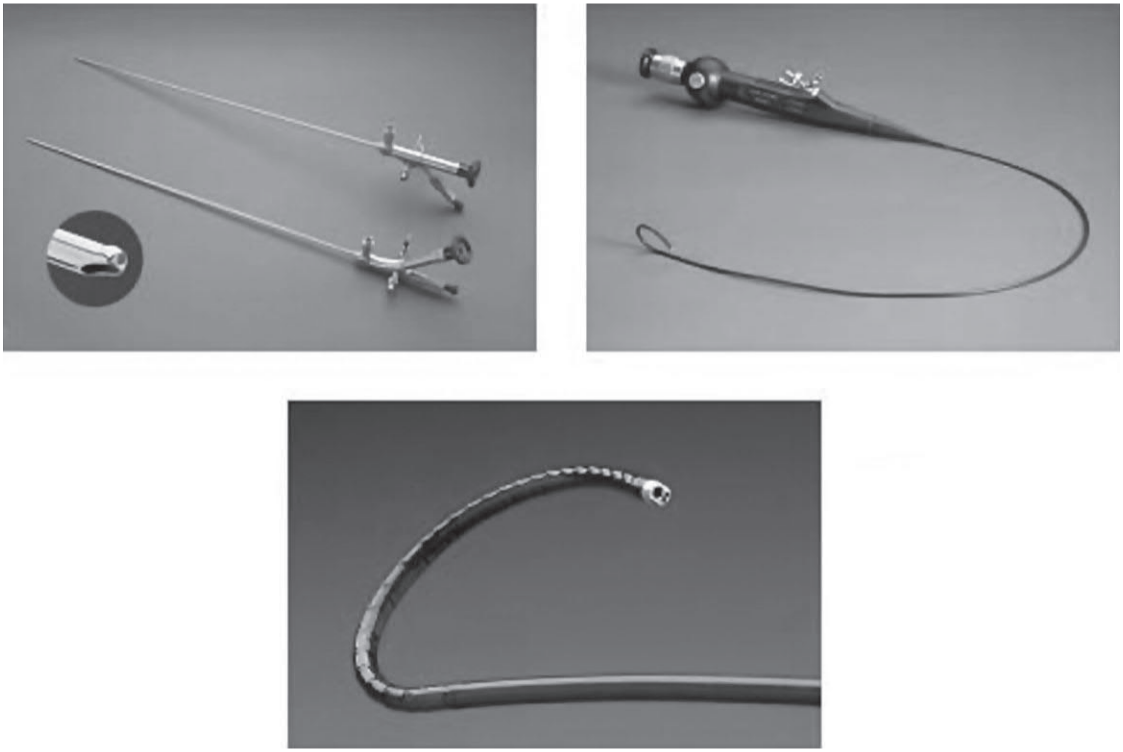
recurrence for clinical T1 renal masses between 4 and 7 cm in size.

Other techniques with limited animal and clinical experience that remain experimental include high-intensity focused ultrasound (HIFU), microwave thermotherapy (MT), laser interstitial thermotherapy (LITT), pulsed cavitational ultrasound, chemoablation with or without radiofrequency, and radiosurgery.

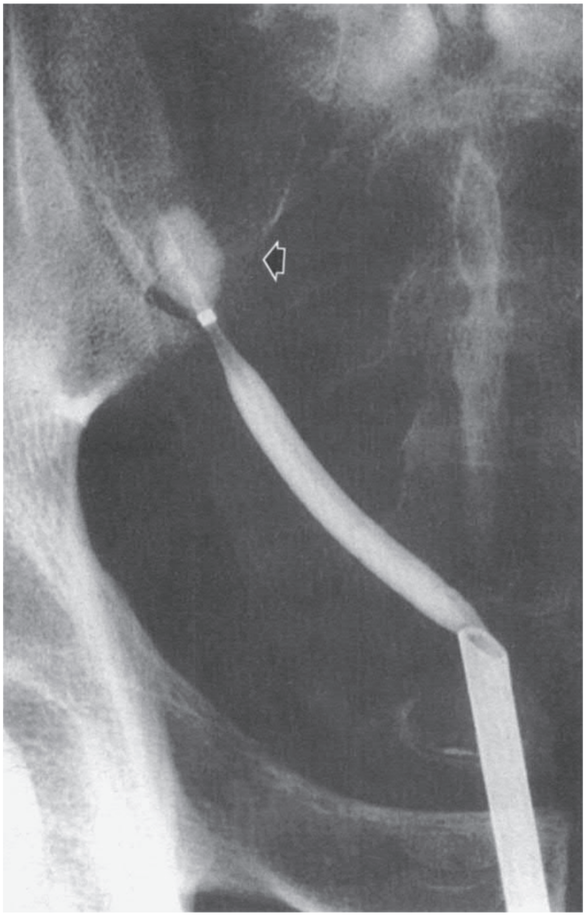
URETERORENOSCOPY

Ureterorenoscopy is endoscopy of the ureter up to the renal pelvis for both diagnostic evaluation and therapeutic intervention (Table 9–4).

Ureterorenoscopes (Figure 9–12) are endoscopes for retrograde insertion into the ureter; however, they may also be used in an antegrade fashion via a percutaneously established nephrostomy tract. Technical improvements in the last decade have led to the introduction of smaller caliber, more versatile instruments. As a result of this progress, the ureterorenoscopic approach is used more widely, not only for management of urinary calculi but also for treatment of urothelial tumors. Rigid ureterorenoscopes are available in sizes of 7–12Fr; and semirigid fiberoptic ureterorenoscopes and flexible ureterorenoscopes, in sizes of 6–9Fr. The smallest instruments are for diagnostic procedures only. Larger instruments, with a 3–6Fr working channel, can accept stone baskets; wire graspers; stone forceps; biopsy forceps; and ultrasonic, electrohydraulic, or laser probes for stone disintegration. Flexible ureterorenoscopes follow the topographic anatomy of the ureter more easily and facilitate inspection of middle and lower renal calyces if a deflecting mechanism for the tip of the instrument is provided. Newer state-of-the-art flexible ureterorenoscopes, both disposable and reusable, have 270° deflecting tips (dual active deflection) that allow access to virtually every calyx of the collecting system. However, the use of instrumentation through flexible nephroscopes is limited by the size and flexibility of working instruments such as



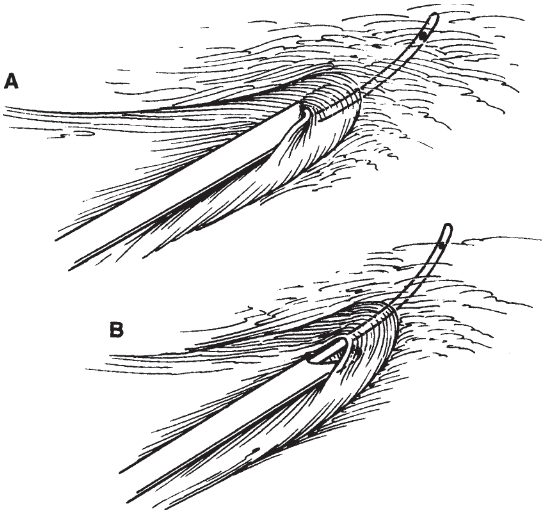
▲ **Figure 9–12.** Various ureteroscopes.



▲ **Figure 9–13.** Fluoroscopic image showing balloon dilation of ureteral stricture.

stone forceps, and flexible ureterorenoscopes do not offer the optical quality and durability of rigid instruments.

Insertion of a ureterorenoscope into the ureteral orifice may be facilitated by dilation of the intramural ureter, with either (1) sequential plastic dilators of increasing size, which are slid over a guidewire, or (2) a balloon dilator catheter (Figure 9–13). Dilation of the ureter is often unnecessary if a ureteral guidewire is inserted through the working channel of the ureterorenoscope into the ureter as a guide, and the ureterorenoscope is then rotated 180° and introduced in an upside-down orientation (Figure 9–14). In this position, the ureteral catheter will spread the roof of the intramural ureter like a tent, and the nose of the instrument will slide flat on the trigone into the orifice. The orifice and intramural ureter will thus be dilated only to the extent necessary for insertion of the instrument.



▲ **Figure 9–14.** 180 degree rotation of ureteroscope facilitating passage through the ureteral orifice.

▶ Diagnostic Ureterorenoscopy

Indications for diagnostic ureterorenoscopy are those rare lesions of the ureter or renal pelvis whose nature cannot be determined with less invasive diagnostic procedures such as retrograde pyelography, selective urinary cytology, CT, or MRI. If a small ureterorenoscope without a working channel is used for a diagnostic procedure, a biopsy of a lesion cannot be obtained. If ureterorenoscopy is performed for evaluation of hematuria from the upper tract, the source of bleeding can rarely be identified during gross hematuria because of limited irrigation through ureterorenoscopes, resulting in poor visibility. If the urine has cleared, the chances of identifying a lesion that could not be detected on radiographic studies are small as well.

▶ Ureteral Stones

Ureterorenoscopy is most frequently performed for treatment of ureteral stones. For the remaining indications of ureteral stone treatment, ureterorenoscopy is used for extraction of stones, repositioning of stones into the renal pelvis for subsequent SWL, and intraureteral stone disintegration. Growing experience in general ureteroscopic techniques and the use of smaller-caliber instruments have also rendered the procedure practicable and safe in the pediatric population, with no evidence of decreasing renal function, and/or renal growth or initiation of vesicoureteral reflux after the procedure.

For extraction of a distal ureteral stone, a short rigid ureterorenoscope and alligator forceps or retrieval basket approach are most helpful. Ureteroscopic clearance rates for distal ureteral stones approach 93–100%. Impacted proximal ureteral stones that did not respond to in situ SWL and could not be mobilized with a ureteral catheter usually can be repositioned into the renal pelvis under direct vision for subsequent SWL using a small semirigid or rigid ureterorenoscope. If the stones are too large or impacted, intraureteral lithotripsy for stone disintegration may become necessary. Flexible ureteroscopic instrumentation in the upper ureter and the necessity to pass and withdraw the ureteroscope repeatedly to extract stone fragments bear an increased risk of injury to the ureter. The ureteral access sheath has been developed to facilitate ureteral reentry and to allow multiple reinsertions of the ureterorenoscope into the upper urinary tract while reducing trauma to the distal ureter. The introducer sheath is available in sizes of 9–16Fr. The better drainage of irrigation fluid from the introducer sheath allows endoscopy to be performed with increased irrigation flow rates, thus enhancing visualization of the upper urinary tract while maintaining low (<40 cm) intrapelvic pressures. Use of an introducer sheath may also decrease wear on the ureteroscope and reduce operative time. However, controversy exists regarding a possible risk of ureteral injury from placement of the working sheath resulting in ureteral stricture rates of 1.4%, which, however, are still in the range of modern series of flexible ureteroscopy without the introducer sheath.

To prevent pushing back of stones or fragments into the renal pelvis during lithotripsy, a 3Fr wire basket can be used to hold the stone during disintegration, or a 3Fr balloon catheter can be passed alongside the stone and blocked proximally. Stone antiretropulsion devices can be used in the same fashion. Ultrasound probes allow safe stone disintegration under continuous suction, but they are not as effective as electrohydraulic and laser probes and can be used through rigid ureterorenoscopes only. Pneumatic probes are thinner and very effective, and require rather inexpensive equipment, but can be used only through rigid and semirigid ureterorenoscopes. Both electrohydraulic and laser probes can be used through rigid or flexible ureterorenoscopes. Laser probes for intraureteral lithotripsy have the smallest diameter (<1Fr) and do not harm the mucosa of the ureter if used under direct vision. Several pulsed lasers such as the holmium:YAG laser, the pulsed-dye laser, and the Alexandrite laser are available for intraureteral lithotripsy. The holmium:YAG laser is most widely used for ureteroscopic lithotripsy because of its high efficiency. It can successfully disintegrate stones of any composition with stone fragmentation rates approaching 100%. Moreover, it can be used to coagulate, ablate, and incise tissues. Laser probes are flexible and as small as 200 μm in core diameter so that they can be easily passed through flexible ureteroscopes without hindering tip deflection and, thus, maximize their durability. Electrohydraulic probes, which are available in sizes of 1.6–5Fr, require less expensive equipment, but they bear the risk of ureteral damage if used inappropriately. The combination of flexible ureteroscopy with atraumatic ancillary tools, such as nitinol tipless baskets and thin holmium laser fibers (200 μm), permits ureteroscopic treatment of renal stones. A 79–90% success rate has been reported for lower pole stones treated ureteroscopically. However, success is highly dependent on number of stones and stone size, and multiple procedures may be required. If ureteral perforation occurs as a complication of intraureteral instrumentation, ureteral stenting using a 6–8Fr double-J stent for 2–6 weeks usually allows healing without late sequelae. Stents should be used for a few days even after uncomplicated ureterorenoscopy to prevent pain from urinary stasis because of edema of the intramural ureter after instrumentation. If there is ureteral perforation and a stent has been placed, the bladder should be on continuous drainage for a few days using a transurethral Foley catheter or a suprapubic cystostomy catheter to prevent urinoma formation from vesicoureteral reflux via the double-J stent.

Ureteropelvic Stenosis

Ureteroscopic endopyelotomy of UPJ obstruction is feasible with a cold knife, electrocautery, or holmium laser. Success rates range between 73% and 90% in different series. However, subsequent repeat balloon dilation of the UPJ may be required in 10% of cases, and 3% may even require repeat incision. At least 10% of recurrences are treated by open or laparoscopic surgery. Thus, the advantages of this minimally invasive procedure such as a reduced hospitalization time and convalescence are at the cost of poorer outcomes compared with open or laparoscopic/robotic assisted pyeloplasty. Also, the risk of complications of ureteroscopy, which range between 1% and 15%, such as ureteral perforation, stricture, false passage, ureteral avulsion, bleeding, and sepsis must be weighed against the possible benefits.

In recent years, Acucise endopyelotomy has gained increased attention as an alternative treatment of UPJ obstruction and other postoperative ureteral strictures in selected patients. It is simple and a truly minimally invasive method that can be performed in an ambulatory setting, but it relies on fluoroscopic rather than visual ureteroscopic guidance. The device permits combining balloon dilatation and incision by electrocautery in one step. Overall success rates for UPJ range between 76% and 81%, and even better outcomes are reported in secondary UPJ obstruction. Prognosticators of treatment failure of UPJ are a stricture length >2 cm, <20% split renal function, the presence of either anterior or posterior crossing vessels, and massive hydronephrosis.

Ureteral Strictures

Cold-knife, electrocautery, or laser incision of a stenosis into the periureteral fat should be followed by stenting of the ureter for 4–6 weeks according to Davis' principle of intubated ureterotomy. The intraoperative use of an endoscopic ultrasound probe can provide important information about the exact stricture location and its relation to adjacent structures and, thus, help to direct the incision.

The best results are obtained in ureteral strictures that are a complication of surgery for benign disorders if treatment is established early. Proximal and distal ureteral strictures respond better to endoureterotomy than do midureteral strictures. Longstanding strictures or strictures due to external ureteral compression, radiation damage, or ischemic ureteral necrosis after surgery are not satisfactorily treated by internal ureterotomy. Acucise treatment of ureteral strictures should be reserved for short strictures (<1.5 cm) in a good functioning kidney.

Ureteral Tumors

Endoscopic electroresection and laser coagulation of ureteral tumors are the ureterorenoscopic variants of percutaneous endoscopic treatment of renal pelvis tumors (see sections on endoscopic intrarenal instrumentation and renal pelvis tumor). Endoscopic treatment of urothelial tumors of the upper urinary tract with curative intent is still confined to low-grade/low-stage small tumors in a solitary kidney, bilateral disease, or chronic renal failure. Follow-up ureterorenoscopy allows surveillance of patients after organ-sparing treatment and simultaneous biopsy, if necessary. Although rare, benign fibroepithelioma of the ureter is sufficiently treated by ureterorenoscopic techniques. The same precautions and limitations apply for endoscopic treatment of urothelial cancer of the ureter as listed previously for percutaneous endoscopic treatment of renal pelvis tumors.

BIBLIOGRAPHY

Percutaneous Catheter Placement

Dyer RB et al: Update on interventional uroradiology. Urol Clin North Am 1997;24:623.

Gofrit ON et al: Lateral decubitus position for percutaneous nephrolithotripsy in the morbidly obese or kyphotic patient. J Endourol 2002;16(6):383.

Goodwin WE et al: Percutaneous trocar (needle) nephrostomy in hydronephrosis. JAMA 1955;157:891.

Kaye KW, Goldberg ME: Applied anatomy of the kidney and ureter. Urol Clin North Am 1982;9:3.

Lau MWM et al: Urinary tract obstruction and nephrostomy drainage in pelvic malignant disease. Br J Urol 1995;76:565.

Pedersen JF: Percutaneous nephrostomy guided by ultrasound. J Urol 1974;112:157.

See WA: Continuous antegrade infusion of Adriamycin as adjuvant therapy for upper tract urothelial malignancies. Urology 2000;56(2):216.

Seldinger SI: Catheter replacement of the needle in percutaneous arteriography. Acta Radiol 1953;39:368.

Smith AD, Badlani GH: Special use of retrograde percutaneous nephrostomy in endourology. J Endourol 1987;1:23.

Tekin MI et al: Practical approach to terminate urinary extravasation: Percutaneous fistula tract embolization with *N*-butyl cyanoacrylate in a case with partial nephrectomy. Tech Urol 2001;7(1):67.

Thüroff JW, Alken P: Ultrasound for renal puncture and fluoroscopy for tract dilatation and catheter placement: A combined approach. Endourology 1987;2:1.

Thüroff JW, Becht E: Urologist's ultrasound. In: Lytton B et al (eds): Advances in Urology, Vol. 1. Year Book Medical Publishers, 1988.

Antegrade Pyelography and Pressure/Perfusion Studies

Ahlawat R, Basarge N: Objective evaluation of the outcome of endopyelotomy using Whitaker's test and diuretic renography. Br J Urol 1995;76:686.

Jones A et al: Compliance studies, pressure flow measurements and renal function assessment in patients with upper urinary tract dilatation. J Urol 1987;138:571.

Kashi SH et al: Does the Whitaker test add to antegrade pyelography in the investigation of collecting system dilatation in renal allografts? Br J Radiol 1993;66:877.

Pagne S, Ramsay J: The effect of double-J-stents on renal pelvic dynamics in the pig. J Urol 1988;140:637.

Whitaker RH: Methods of assessing obstruction in dilated ureters. Br J Urol 1973;45:15.

Whitaker RH, Buxton-Thomas MS: A comparison of pressure flow studies and renography in equivocal upper urinary tract obstruction. J Urol 1984;131:446.

Woodburg P et al: Constant pressure perfusion: A method to determine obstruction in the upper urinary tract. J Urol 1989;142:632.

Percutaneous Renal Stone Treatment

Albala DM et al: Lower pole I: A prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis: Initial results. J Urol 2001;166(6):2072.

Alken P et al: Percutaneous nephrolithotomy: A routine procedure? Br J Urol 1983;51(Suppl):1.

Calvert RC, Burgess NA: Urolithiasis and obesity: Metabolic and technical considerations. Curr Opin Urol 2005;15(2):113.

Cato AR, Tulloch AGS: Hypermagnesemia in a uremic patient during renal pelvis irrigation with Renacidin. J Urol 1974;111:313.

Chatham JR et al: Effect of percutaneous nephrolithotomy on differential renal function as measured by mercaptoacetyl triglycine nuclear renography. Urology 2002;59(4):522, discussion 525.

Desai MR et al: A prospective randomized comparison of type of nephrostomy drainage following percutaneous nephrostolithotomy: Large bore versus small bore versus tubeless. J Urol 2004;172(2):565.

el-Damanhoury H et al: Surgical aspects of urolithiasis in children. Pediatr Nephrol 1991;5:339.

Falahatkar S, Allahkhah A, Kazemzadeh M, Enshaei A, Shakiba M, Moghaddas F: Complete supine PCNL: Ultrasound vs. fluoroscopic guided: a randomized clinical trial. Int Braz J Urol 2016;42(4):710–716.

Feng MI et al: Prospective randomized study of various techniques of percutaneous nephrolithotomy. Urology 2001;58(3):345.

Fernström I, Johansson B: Percutaneous pyelolithotomy: A new extraction technique. Scand J Urol Nephrol 1976;10:257.

Heimbach D et al: Percutaneous chemolysis: An important tool in the treatment of urolithiasis. Int Urol Nephrol 1998;30(6):655.

Holman E et al: Simultaneous bilateral compared with unilateral percutaneous nephrolithotomy. BJU Int 2002;89(4):334.

Hudnall M, Usawachintachit M, Metzler I, Tzou DT, Harrison B, Lobo E, Chi T: Ultrasound guidance reduces percutaneous nephrolithotomy cost compared to fluoroscopy. Urology 2017;103: 52–58.

Jou YC et al: Nephrostomy tube-free percutaneous nephrolithotomy for patients with large stones and Staghorn stones. Urology 2006;67(1):30.

Lahme S et al: Minimally invasive PCNL in patients with renal pelvic and calyceal stones. Eur Urol 2001;40(6):619.

Limb J, Bellman GC: Tubeless percutaneous renal surgery: Review of first 112 patients. Urology 2002;59(4):527, discussion 531.

Minon Cifuentes J et al: Percutaneous nephrolithotomy in transplanted kidney. Urology 1991;38:232.

Osman M et al: Percutaneous nephrolithotomy with ultrasonography-guided renal access: Experience from over 300 cases. BJU Int 2005;96(6):875.

Pathak AS, Bellman GC: One-step percutaneous nephrolithotomy sheath versus standard two-step technique. Urology 2005; 66(5):953.

Ramakumar S, Segura JW: Renal calculi: Percutaneous management [review]. Urol Clin North Am 2000;27(4):617.

Rao PN et al: Prediction of septicemia following endourological manipulation for stones in the upper urinary tract. J Urol 1991;146:955.

Schwartz BF, Stoller M: Percutaneous management of caliceal diverticula [review]. Urol Clin North Am 2000;27(4):635.

Segura JW et al: Percutaneous removal of kidney stones: Review of 1000 cases. J Urol 1985;134:1077.

Segura JW: The role of percutaneous surgery in renal and ureteral stone removal. J Urol 1989;141(Pt 2 of 2):780.

Segura JW: Role of percutaneous procedures in the management of renal calculi. Urol Clin North Am 1990;17:207.

Suby HI, Albright F: Dissolution of phosphatic urinary calculi by the retrograde introduction of citrate solution containing magnesium. N Engl J Med 1943;228:81.

Thüroff JW, Alken P: Stones in caliceal diverticula: Removal by percutaneous nephrolithotomy. In: Jonas U et al (eds): Endourology: New and Approved Techniques. Springer-Verlag, 1988.

Usawachintachit M, Tzou DT, Hu W, Li J, Chi T: X-ray-free ultrasound-guided percutaneous nephrolithotomy: How to select the right patient? Urology 2017;100:38–44.

Wong MY: An update on percutaneous nephrolithotomy in the management of urinary calculi [review]. Curr Opin Urol 2001;11(4):367.

Percutaneous Endoscopic Surgery

American Urological Association: Guideline for Management of the Clinical Stage 1 Renal Mass. (Available online at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/renalmass09.pdf; accessed 9/22/09.)

Aron M, Gill IS: Renal tumor ablation. Curr Opin Urol 2005;15(5):298.

Aslan P, Preminger GM: Retrograde balloon cautery incision of ureteropelvic junction obstruction. Urol Clin North Am 1998;25:295.

Berger A et al: Cryoablation for renal tumors: current status. Curr Opin Urol 2009;19:138.

Bernardo NO, Smith AD: Percutaneous endopyelotomy. Urology 2000;56:322.

Chan Y, Durbin Johnson B, Sturm RM, Kurzrock EA: Outcomes after pediatric open, laparoscopic, and robotic pyeloplasty at academic institutions. J Pediatr Urol 2017;13(1):49.e1–49.e6.

Chow WH et al: Rising incidence of renal cell cancer in the United States. JAMA 1999;281(17):1628.

Danuser H et al: Endopyelotomy for primary ureteropelvic junction obstruction: Risk factors determine the success rate. J Urol 1998;159(1):56.

Danuser H et al: Influence of stent size on the success of antegrade endopyelotomy for primary ureteropelvic junction obstruction: Results of 2 consecutive series. J Urol 2001;166(3):902.

Davis DM: Intubated ureterotomy: A new operation for ureteral and ureteropelvic strictures. Surg Gynecol Obstet 1943;76:513.

Delakas D et al: Long-term results after percutaneous minimally invasive procedure treatment of symptomatic simple renal cysts. Int Urol Nephrol 2001;32(3):321.

Delvecchio FC et al: Combined antegrade and retrograde endoscopic approach for the management of urinary diversion-associated pathology. J Endourol 2000;14(3):251.

Figenshau RS, Clayman RV: Endourologic options for management of ureteropelvic junction obstruction in the pediatric patient. Urol Clin North Am 1998;25:199.

Gill IS: Renal cryotherapy: Pro. Urology 2005;65(3):415.

Gill IS, et al: Renal cryoablation: Outcome at 3 years. J Urol 2005; 173(6):1903.

Goldfischer ER, Smith AD: Endopyelotomy revisited. Urology 1998; 51:855.

Hauser S, Studer UE: Therapy of carcinoma of the kidney pelvis. Urologe A 2001;40(6):452.

Hibi H et al: Retrograde ureteroscopic endopyelotomy using the holmium:YAG laser. Int J Urol 2002;9(2):77.

Hulbert JC et al: Percutaneous intrarenal marsupialization of a perirenal cystic collection: Endocystolysis. J Urol 1988;139:1039.

Hvarness H et al: Long-term remission of transitional cell carcinoma after Bacillus Calmette-Guérin instillation in the renal pelvis. J Urol 2001;166(5):1829.

Jabbour ME et al: Percutaneous management of grade II upper urinary tract transitional cell carcinoma: The long-term outcome. J Urol 2000;163:1105.

Kapoor R et al: Endopyelotomy in poorly functioning kidney: Is it worthwhile? J Endourol 2001;15(7):725.

Kumar R et al: Optimum duration of splinting after endopyelotomy. J Endourol 1999;13(2):89.

Kunkle DA et al: Excise, ablate or observe: The small renal mass dilemma—A meta-analysis and review. J Urol 2008;179:1227.

McAchran SE et al: Radiofrequency ablation of renal tumors: Past, present, and future. Urology 2005;66(5A):15.

Meretyk I et al: Endopyelotomy: Comparison of ureteroscopic retrograde and antegrade percutaneous techniques. J Urol 1992; 148:775.

Nakada SY et al: Retrospective analysis of the effect of crossing vessels on successful retrograde endopyelotomy outcomes using spiral computerized tomography angiography. J Urol 1998;159:62.

Okubo K et al: Intrarenal bacillus Calmette-Guérin therapy for carcinoma in situ of the upper urinary tract: Long-term follow-up and natural course in cases of failure. BJU Int 2001;88(4):343.

Potter SR et al: Percutaneous endoscopic management of urothelial tumors of the renal pelvis. Urology 2001;58(3):457.

Rosdy E: Percutaneous transrenal ureteroneocystostomy. J Endourol 1999;13(5):369.

Savage SJ, Streem SB: Simplified approach to percutaneous endopyelotomy. Urology 2000;56:848.

Schenkman EM, Terry WF: Comparison of percutaneous endopyelotomy with open pyeloplasty for pediatric ureteropelvic junction obstruction. J Urol 1998;159:1013.

Schwartz BF et al: Treatment of refractory kidney transplant ureteral strictures using balloon cautery endoureterotomy. Urology 2001;58(4):536.

Segura JW: Antegrade endopyelotomy. Urol Clin North Am 1998;25:311.

Shalhav AL et al: Adult endopyelotomy: Impact of etiology and antegrade versus retrograde approach on outcome. J Urol 1998;160:685.

Shalhav AL et al: Endopyelotomy for high-insertion ureteropelvic junction obstruction [review]. J Endourol 1998;12(2):127.

Sterrett SP et al: Renal thermal ablative therapy. Urol Clin North Am 2008;35:397.

Streem SB: Percutaneous endopyelotomy [review]. Urol Clin North Am 2000;27(4):685, ix.

Van Cangh PJ, Nesa S: Endopyelotomy. Urol Clin North Am 1998;25:281.

Watterson JD et al: Holmium:YAG laser endoureterotomy for ureterointestinal strictures. J Urol 2002;167(4):1692.

Weizer AZ et al: Complications after percutaneous radiofrequency ablation of renal tumors. Urology 2005;66(6):1176.

Wolf JS: Retrograde Acucise endopyelotomy. Urology 1998;51:859.

Yohannes P, Smith AD: The endourological management of complications associated with horseshoe kidney. J Urol 2002;168(1):5.

Percutaneous Aspiration and Biopsy

Bodner L et al: The role of interventional radiology in the management of intra- and extra-peritoneal leakage in patients who have undergone continent urinary diversion. Cardiovasc Intervent Radiol 1997;20:274.

Bush WH Jr et al: Needle tract seeding of renal cell carcinoma. Am J Roentgenol 1977;129:725.

Caputo PA, Zargar A, Ramirez D, Andrade HS, Akca O, Gao T, Kaouk JH: Cryoablation versus partial nephrectomy for clinical T1b renal tumors: A matched group comparative analysis. Eur Urol 2017;71(1):111–117.

Coptcoat MJ et al: Endoscopic tissue liquidization and surgical aspiration. J Endourol 1988;2:321.

De Dominicis C et al: Percutaneous sclerotization of simple renal cysts with 95% ethanol followed by 24–48 h drainage with nephrostomy tube. Urol Int 2001;66(1):18.

Diaz-Buxo JA, Donadio JV Jr: Complications of percutaneous renal biopsy: An analysis of 1,000 consecutive biopsies. Clin Nephrol 1975;4:223.

Ferrucci JT et al: Malignant seeding of the tract after thin-needle aspiration biopsy. Radiology 1979;130:345.

Gibbons RP et al: Needle tract seeding following aspiration of renal cell carcinoma. J Urol 1977;118:865.

Hara I et al: Role of percutaneous image-guided biopsy in the evaluation of renal masses. Urol Int 2001;67(3):199.

Michael JM et al: Angiomyolipoma of the renal sinus: Diagnosis by percutaneous biopsy. Urology 2000;55(2):286.

Sadi MV et al: Percutaneous drainage of retroperitoneal abscesses. J Endourol 1988;2:293.

Stiles KP et al: The impact of bleeding times on major complication rates after percutaneous real-time ultrasound-guided renal biopsies. J Nephrol 2001;14(4):275.

Wehle MJ, Grabstald H: Contraindications to needle aspiration of a solid renal mass: Tumor dissemination by renal needle aspiration. J Urol 1986;136:446.

Stone Basketing, Ureterorenoscopy

Abrahams HM, Stoller ML: The argument against the routine use of ureteral access sheaths. Urol Clin North Am 2004;31(1):83.

Al-Awadi KA et al: Steinstrasse: A comparison of incidence with and without "J" stenting and the effect of "J"' stenting on subsequent management. BJU Int 1999;84:618.

Bagley DH: Ureteroscopic surgery: Changing times and perspectives. Urol Clin North Am 2004;31(1):1.

Borboroglu PC et al: Ureteral stenting after ureteroscopy for distal ureteral calculi: A multi-institutional prospective randomized controlled study assessing pain, outcomes and complications. J Urol 2001;166(5):1651.

Busby JE, Low RK: Ureteroscopic treatment of renal calculi. Urol Clin North Am 2004;31(1):89.

Chen CL, Bagley DH: Ureteroscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidneys. J Urol 2000;164:1173.

Conlin MJ et al: Ureteroscopy, development and instrumentation. Urol Clin North Am 1997;24:25.

Delvecchio FC et al: Assessment of stricture formation with the ureteral access sheath. Urology 2003;61(3):518.

Denstedt JD et al: A prospective randomized controlled trial comparing nonstented versus stented ureteroscopic lithotripsy. J Urol 2001;165(5):1419.

Dourmashkin RL: Cystoscopic treatment of stones in the ureter with special reference to large calculi: Based on a study of 1550 cases. J Urol 1945;54:245.

Dretler SP: Clinical experience with electromechanical impactor. J Urol 1993;150:1402.

Dretler SP: The stone cone: A new generation of basketry. J Urol 2001;165(5):1593.

El-Anany FG et al: Retrograde ureteropyeloscopic holmium laser lithotripsy for large renal calculi. BJU Int 2001;88(9):850.

Gettman MT, Segura JW: Management of ureteric stones: Issues and controversies. BJU Int 2005;95(Suppl 2):85.

Goldfischer ER, Gerber GS: Endoscopic management of ureteral strictures. J Urol 1997;157:770.

Grasso M et al: Ureteropyeloscopic diagnosis and treatment of upper urinary tract urothelial malignancies. Urology 1999;54:240.

Grasso M, Ficazzola M: Retrograde ureteropyeloscopy for lower pole caliceal calculi. J Urol 1999;162(11):1904.

Hafner C et al: Evidence for oligoclonality and tumor spread by intraluminal seeding in multifocal urothelial carcinomas of the upper and lower urinary tract. Oncogene 2001;20(35):4910.

Hara I et al: Usefulness of ureteropyeloscopy for diagnosis of upper urinary tract tumors. J Endourol 2001;15(6):601.

Hennessey DB, Fojecki GL, Papa NP, Lawrentschuk N, Bolton D: Single-use disposable digital flexible ureteroscopes: an ex vivo assessment and cost analysis. BJU Int 2018;121(Suppl 3): 55–61.

Hollenbeck BK et al: Flexible ureteroscopy in conjunction with in situ lithotripsy for lower pole calculi. Urology 2001;58(6):859.

Hosking DH et al: Is stenting following ureteroscopy for removal of distal ureteral calculi necessary? J Urol 1999;161(1):48.

Krambeck AE et al: The evolution of ureteroscopy: A modern single-institution series. Mayo Clin Proc 2006;81(4):468.

Kourambas J et al: Dose a ureteral access sheath facilitate ureteroscopy? J Urol 2001;165(3):789.

Lam JS, Gupta M: Ureteroscopic management of upper tract transitional cell carcinoma. Urol Clin North Am 2004;31(1):115.

Larizgoitia I, Pons JMV: A systematic review of the clinical efficacy and effectiveness of the holmium:YAG laser in urology. BJU Int 1999;84:1.

Lechevallier E et al: Retrograde Acucise endopyelotomy: Long term results. J Endourol 1999;13:575.

Mendez-Torres FR et al: Retrograde ureteroscopic endopyelotomy. Urol Clin North Am 2004;31(1):99.

Nakada SY et al: Long-term outcome of flexible ureterorenoscopy in the diagnosis and treatment of lateralizing essential hematuria. J Urol 1997;157:776.

Nakada SY: Acucise endopyelotomy. Urology 2000;55(2):277.

Netto NR et al: Ureteroscopic stone removal in the distal ureter. Why change? J Urol 1997;157:2081.

Patel RC, Newman RC: Ureteroscopic management of ureteral and ureteroenteral strictures. Urol Clin North Am 2004; 31(1):107.

Richter F et al: Endourologic management of benign ureteral strictures with and without compromised vascular supply. Urology 2000;55:652.

Schuster TG et al: Ureteroscopy for the treatment of urolithiasis in children. J Urol 2002;167(4):1813.

Seseke F et al: Treatment of iatrogenic postoperative ureteral strictures with Acucise endoureterotomy. Eur Urol 2002;42(4):370.

Singal RK, Denstedt JD: Contemporary management of ureteral stones. Urol Clin North Am 1997;24:59.

Sofer M et al: Holmium:YAG laser lithotripsy for upper urinary tract calculi in 598 patients. J Urol 2002;167:31.

Thomas R et al: Safety and efficacy of pediatric ureteroscopy for management of calculous disease. J Urol 1993;149:1082.

Vanlangendonck R, Landman J: Ureteral access strategies: Pro-access sheath. Urol Clin North Am 2004;31(1):71.

Zheng W, Denstedt JD: Intracorporeal lithotripsy: Update on technology. Urol Clin North Am 2000;27:301.

Laparoscopic Surgery

10

David B. Bayne, MD, MPH; J. Stuart Wolf, Jr., MD, FACS;
Marshall L. Stoller, MD; & Thomas Chi, MD

Laparoscopy plays a prominent role in urology, a field that saw early adoption of these minimally invasive techniques starting with laparoscopic nephrectomy. Approaches and techniques in laparoscopy have evolved significantly over time, and the use of laparoscopy for surgery across organ systems has expanded. Alternatives to standard laparoscopy, including hand assistance and robotic assistance, further enhance capabilities.

PHYSIOLOGY OF LAPAROSCOPY

Laparoscopy with pneumoperitoneum exposes the patient to physiologic challenges that differ from those of open surgery but that can be met successfully with proper preparation and awareness (Ost et al, 2005).

Cardiovascular Physiology

As intra-abdominal pressure increases with pneumoperitoneum, the systemic vascular resistance increases and venous return decreases. A small increase in intra-abdominal pressure augments venous return and cardiac output. As intra-abdominal pressure rises, the increase in resistance exceeds the increase in pressure, and venous return and cardiac output fall (Figure 10–1). This transition point occurs at a lower intra-abdominal pressure in the hypovolemic compared with the normovolemic state. Given normovolemia, an intra-abdominal pressure of 15 mm Hg is associated with tolerable reduction of cardiac output.

The absorption of insufflated carbon dioxide (CO_2) has direct cardioinhibitory effects, but CO_2 also stimulates the sympathetic nervous system. If acidosis develops, then there are parasympathetic effects as well. Moderate hypercapnia (excess CO_2 in blood) produces an increase in cardiac output and blood pressure and a decrease in systemic vascular resistance, which counteract the effect of intra-abdominal pressure.

Overall, an intra-abdominal pressure of 15 mm Hg and moderate hypercapnia in healthy patients produce a hyperdynamic state (increased central venous pressure, systemic vascular resistance, heart rate, and blood pressure) without significant alteration of cardiac output (Junghans et al, 2005).

Cardiovascular Physiological Complications

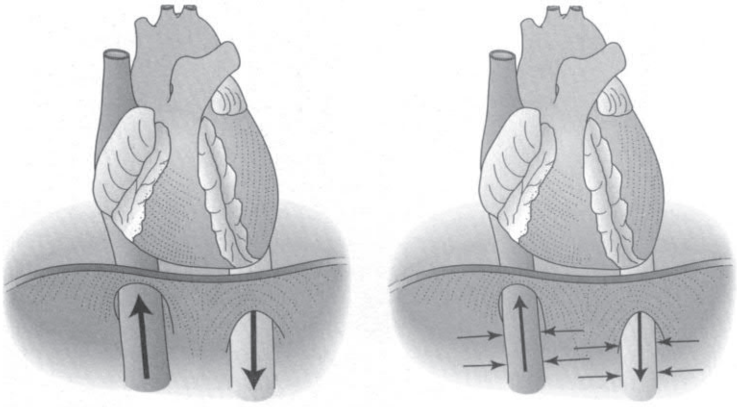
The cardiovascular complications of laparoscopy include tension pneumoperitoneum, cardiac dysrhythmias, fluid overload, and venous thrombosis.

When the intra-abdominal pressure is excessive, usually >40 mm Hg, the overwhelming increase of vascular resistance can produce **tension pneumoperitoneum**. This state can occur with loss of neuromuscular paralysis, for example, intraoperatively. Venous return, cardiac output, and blood pressure drop precipitously. Volume status must be optimized to prevent tension pneumoperitoneum at lower pressures. In general, the intra-abdominal pressure should be kept below 15–20 mm Hg. The response to tension pneumoperitoneum should be immediate desufflation.

Tachycardia and ventricular extrasystoles due to hypercapnia are usually benign, but fatal dysrhythmias can occur with very high arterial partial pressure of CO_2 ($PaCO_2$). Vagal stimulation by peritoneal distention can produce bradydysrhythmias (Valentin et al, 2004).

Because insensible fluid losses and urine output are less during laparoscopy than during open surgery, after optimizing volume status before insufflation intraoperative fluid administration should be limited to appropriate replacement for blood loss plus a maintenance rate of 5 mL/kg per hour to avoid volume overload.

Since increased abdominal pressure during laparoscopy restricts lower extremity venous return, thromboembolism prophylaxis protocol should be utilized for urological laparoscopic and robotically assisted urologic laparoscopic procedures with recommendation for intermittent pneumatic



▲ **Figure 10–1.** Reduction of venous return and cardiac output during laparoscopy. (Adapted with permission from Wolf JS Jr, Stoller ML: The physiology of laparoscopy: basic principles, complications and other considerations, J Urol. 1994 Aug;152(2 Pt 1):294–302.)

compression devices and low-dose subcutaneous heparin in high-risk groups (Forrest et al, 2009).

Pulmonary, Acid–Base, and Insufflant-Related Physiology

Increased intra-abdominal volume elevates the diaphragm, which reduces lung capacity and compliance. Insufflated CO_2 diffuses into the bloodstream. The amount of CO_2 absorbed during intraperitoneal CO_2 laparoscopy at typical pressures is equivalent to adding 5–25% to the body's baseline production of CO_2. Subcutaneous emphysema, elevated intra-abdominal pressure, extraperitoneal insufflation, and increased duration of insufflation all increase the rate of CO_2 absorption.

Pulmonary, Acid–Base, and Insufflant-Related Physiological Complications

The pulmonary, acid–base, and insufflant-related complications of laparoscopy include hypercapnia, acidosis, extraperitoneal gas collections, and venous gas embolism (VGE).

Moderate hypercapnia is stimulatory overall, but if $PaCO_2$ exceeds 60 mm Hg, then potentially lethal cardiodepressive effects predominate. Increasing ventilation rate and tidal volume adequately eliminates excess CO_2 in most patients. $PaCO_2$ is estimated intraoperatively by the partial pressure of end-tidal CO_2 ($P[et]CO_2$) measured with capnometry, which generally is 3–5 mm Hg lower than $PaCO_2$ during general anesthesia. During prolonged operations or in patients with pulmonary disease, the gradient may widen unpredictably, and arterial blood gases should be obtained for accurate monitoring (Kim, 2008).

Absorption of insufflated CO_2 causes a mild respiratory acidosis. With gas insufflation pressures of >20 mm Hg, a metabolic acidosis also can develop, likely related to retained acids from decreased urine output.

Gases insufflated into the peritoneal cavity may leak into several extraperitoneal spaces. Subcutaneous emphysema is the most common site of extraperitoneal gas. Although generally innocuous, it increases the risk of hypercapnia (Saggar et al, 2008). Pneumopericardium, pneumomediastinum, and pneumothorax can inhibit cardiac filling and/or lung excursion. A CO_2 pneumothorax will usually resolve spontaneously, but thoracostomy should be performed for a symptomatic pneumothorax (Msezane et al, 2007).

Venous gas embolism is the passage of gas bubbles through the venous system into the heart and pulmonary circulation (Min et al, 2007). When clinically significant, right heart outflow is impeded, producing hypoxemia, hypercapnia, and depressed cardiac output. Many VGEs that occurred during laparoscopy have been fatal. VGE is indicated by hypoxemia, pulmonary edema, increased airway pressure, hypotension, jugular venous distention, facial plethora, dysrhythmias, and a millwheel murmur. The capnometer will register a sudden fall in $P(et)CO_2$ if the CO_2 embolus is large. Swift response is required, including immediate desufflation, rapid ventilation with 100% oxygen, steep head-down tilt with the right side up, and general resuscitative maneuvers.

SELECTION OF LAPAROSCOPIC APPROACH

There are numerous alternative approaches to laparoscopic surgery. Access can be transperitoneal or retroperitoneal. Options for surgical manipulation include standard laparoscopy, hand assistance, and robotic assistance. Additional modifications have been developed, such as microlaparoscopy, laparoendoscopic single-site surgery (LESS), and natural-orifice translumenal endoscopic surgery (NOTES)

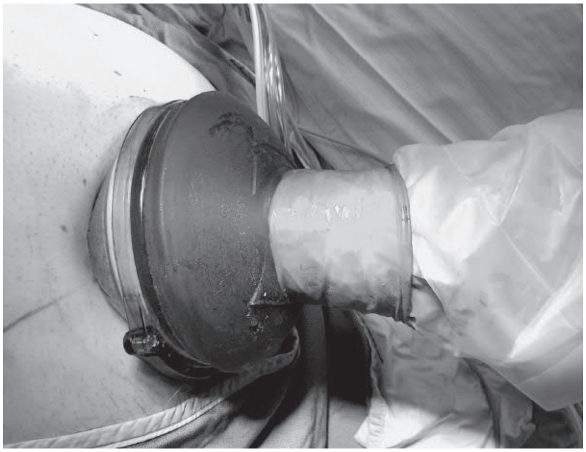
(Kommu et al, 2009; Raman et al, 2008). Only the most common alternatives are described here.

Transperitoneal versus Retroperitoneal

The transperitoneal route provides a capacious workspace and allows direct visualization of familiar intraperitoneal anatomy. It is the most common route for most procedures. Transperitoneal access may be difficult, however, in patients who have had extensive abdominal surgery. The retroperitoneal approach allows easier and more rapid access to the retroperitoneal structures and avoidance of intra-abdominal organs and adhesions. A disadvantage of the retroperitoneal technique is the limited workspace. Comparisons of the two routes for various procedures have shown no consistent difference in operative times, cost, length of stay, or postoperative convalescence (Desai et al, 2005). The approach therefore is dictated by the familiarity of the surgeon and the patient's condition.

Hand Assistance

Hand-assisted laparoscopic surgery (HALS) entails the insertion of a hand through a 7–9-cm incision into the laparoscopic field, while maintaining pneumoperitoneum with a hand assistance device that employs a compressive mechanism to affix to the abdomen and prevent leakage of pneumoperitoneum around the intra-abdominal hand (Figure 10–2). The intra-abdominal hand is used for dissection, tissue identification, retraction, and control of injuries. The benefits of HALS include shorter operative times than for similar standard laparoscopic transperitoneal procedures in many series, ease of learning by inexperienced surgeons, and enhanced ability to manage difficult surgical situations. Additionally, conversion from standard laparoscopy to hand assistance is an alternative to conversion to open surgery. Disadvantages of HALS include problems with the devices (gas leakage or interference with port placement), physical strain on the hand, interference of the hand in the operative field, and the creation of a larger incision (and likely more wound complications) than for a standard laparoscopic procedure (Wolf, 2005). Numerous comparative studies between standard and hand-assisted laparoscopy show generally similar convalescence (Silberstein and Parsons, 2009).



▲ **Figure 10–2.** Surgeon's hand inside Gelport. (Used with permission from Applied Medical, Rancho Santa Margarita, CA.)

Robotic Assistance

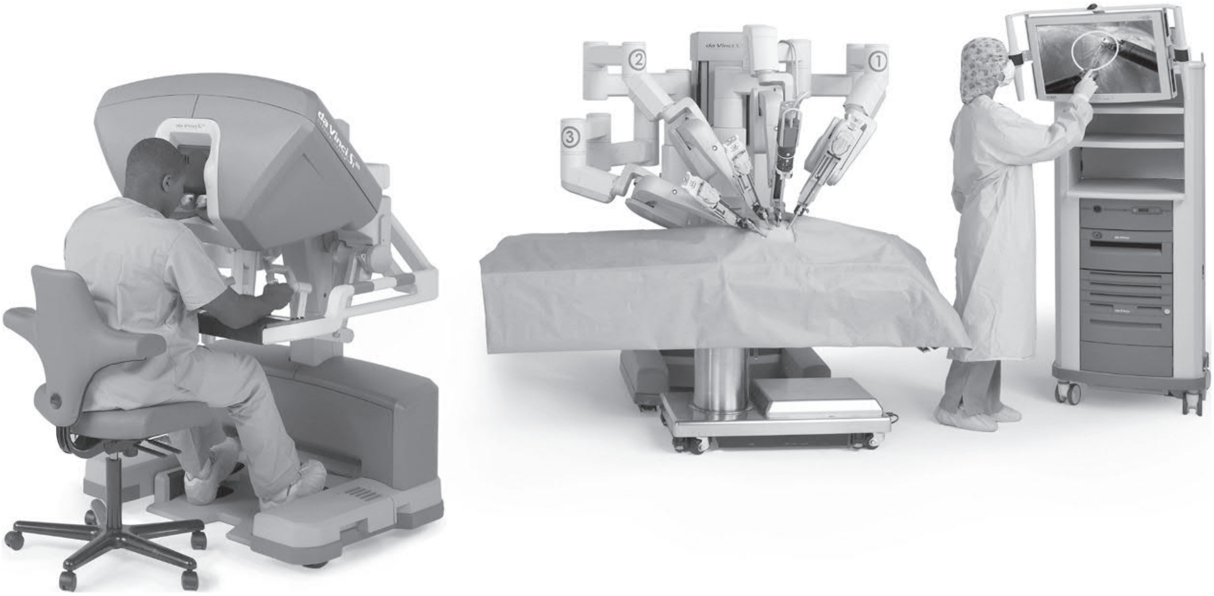
The robot used for laparoscopic surgery has a three-dimensional camera and arms that are directed by the surgeon seated at the control console (Figure 10–3). The most commonly used robot worldwide is the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA). For urology, it has achieved great popularity for application to radical prostatectomy, cystectomy, and renal surgery. The advantages of robotic assistance include easier transference of open surgical skills to laparoscopic surgery, instrument tips with multiple degrees of freedom, and better ergonomics than standard laparoscopy. Disadvantages may include the cost of the system and disposables and the need for a trained assistant at the bedside (Nelson, 2007). While capital expenditures needed to purchase and maintain a robot are high, some data suggest that overall cost of robotic surgery may be mitigated in the long run, given improvement in recovery with postoperative reduction in inpatient admissions and hospitalization days (Hughes et al, 2006).

LAPAROSCOPIC INSTRUMENTATION AND BASIC TECHNIQUES

Preoperative Preparation

Although any operation in a patient with obesity, previous abdominal surgery, or abnormal anatomy is difficult, laparoscopy is relatively more challenged by these factors than is open surgery. In addition, open surgery may be favored physiologically over laparoscopy in patients with severe pulmonary disease or congestive heart failure. The patient who is offered laparoscopy should be fully informed of the risks and benefits, most appropriately in the context of a comparison with the spectrum of risks and benefits of the corresponding open surgery. Inform the patient of the surgeon's experience with the particular laparoscopic procedure, and mention that conversion to open surgery may be required. For transperitoneal laparoscopic surgery without intended bowel resection, patient preparation with a clear liquid diet and oral magnesium citrate on the preoperative day is adequate. For retroperitoneoscopic surgery, bowel preparation is not necessary.

The primary laparoscopic cart (see discussion later) is positioned opposite the surgeon. For an upper abdominal or retroperitoneal procedure, a secondary monitor for nursing staff or assistants placed on the opposite side of the patient is useful. Operating rooms with equipment rooms that extend



▲ **Figure 10–3.** The da Vinci Surgical System. (Used with permission from Intuitive Surgical, Sunnyvale, CA.)

down from the ceiling minimize clutter and reduce setup time. After induction of anesthesia and endotracheal intubation, insert a urethral catheter and orogastric tube. For pelvic surgery, position the patient supine (or in some cases, in dorsal lithotomy position), with the chest securely taped to allow steep Trendelenburg tilt of the table. For transperitoneal procedures into the retroperitoneum, place the patient in partial flank position (45°) without flexion of the table. Direct retroperitoneoscopic procedures benefit from full flank position with table flexion.

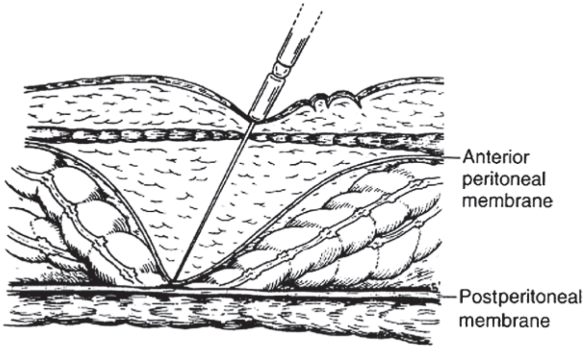
Operative Entry

A. Obtaining Pneumoperitoneum

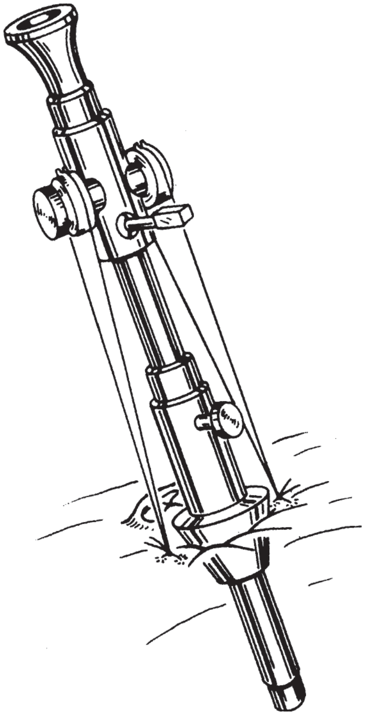
Initial access is commonly obtained with the closed (Veress needle) or open (Hasson cannula) techniques, although instruments that provide direct visualization access are available as well. Any of these approaches is acceptable, but multiple techniques should be learned, since sometimes laparoscopy is contraindicated or fails and another procedure is needed.

The Veress needle has a spring-loaded stylet that retracts back only under pressure from firm tissue (ie, fascia) to expose the sharp cannula; once the tip is free in the intraperitoneal space, the stylet springs forward and protects against visceral injury. The needle is usually placed at the location of the first port, although the site should be moved away from any prior incisions. (Extensive abdominal surgery or suspected dense adhesions are a relative contraindication for Veress needle use.) The needle is inserted almost perpendicular to the abdominal wall, tilting slightly away from the large midline vessels. An exception is when the needle is being placed at the umbilicus in thin individuals, in which case it needs to be angled more acutely.

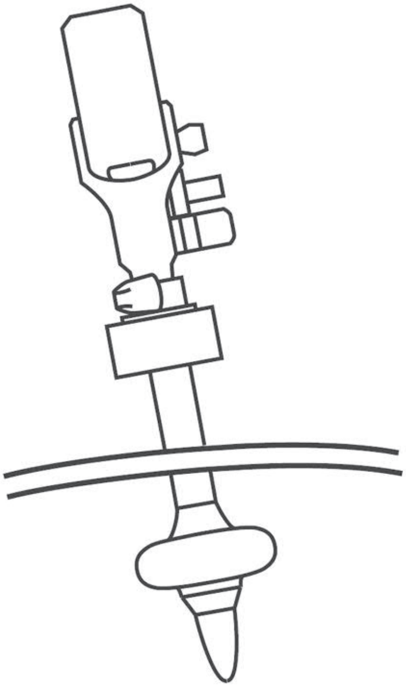
After inserting the needle, attach a 10-mL syringe half-filled with saline and aspirate back. There should be no aspirated gas or liquid. Next, inject saline through the needle and attempt to aspirate. Fluid should flow in easily and not return. Finally, the saline in the hub of the Veress needle should drop rapidly into the abdomen. These maneuvers assess for the possibility that the needle tip is in a luminal structure (bowel, blood vessel, etc), but all will be "normal" if the needle is preperitoneal—which is the most common erroneous placement (Figure 10–4). This possibility is assessed



▲ **Figure 10–4.** Preperitoneal location of the tip of Veress needle.



▲ **Figure 10–5.** Hasson cannula.



▲ **Figure 10–6.** Self-retaining port. (Used with permission from AutoSuture Co, Norwalk, CT.)

by the final test, the "opening pressure" as gas is insufflated. The pressure should not rise above 8 mm Hg within the first 0.5 L of gas, or if it does, it should be only momentary and quickly correctable by a twist, slight withdrawal, and tilting up of the needle (which will free the needle tip from omental or mesenteric fat). If these conditions are met, then continue insufflation, but if not, then disconnect the insufflation tubing, allow the gas to escape, and withdraw the needle.

The Hasson technique consists in placement of a laparoscopic port through a small incision under direct vision. Make a 1.5–3-cm incision down to and through the peritoneal membrane. Place stay sutures, and then insert the Hasson port (10/12 cannula containing a blunt obturator, with a conical adjustable sleeve; Figure 10–5). Tie the sutures to the arms of the device to secure the conical sleeve within the fascia. An alternative port has a retaining balloon that inflates intra-abdominally and is held up tight against the fascia by an adjustable retaining ring (Figure 10–6). Another alternative is to make a smaller incision in the fascia and peritoneal membrane and insert a blunt port that dilates rather than cuts the fascia.

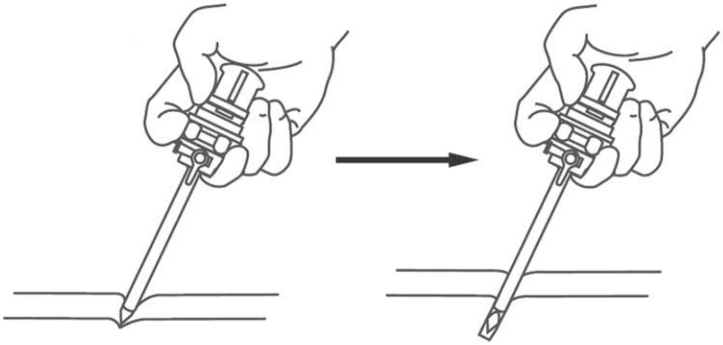
Visualizing trocar systems are designed to be inserted after a skin incision is made. With the assistance of a camera and lens seated into the trocar, the surgeon watches passage of each tissue layer from the dermis past the peritoneum to ensure accurate trocar placement. No prior insufflation is required, and trocar advancement relies on tips that penetrate tissue layers while minimizing trauma to intraabdominal organs.

While each of these entry systems has its advantages and disadvantages, all of them have been associated with unintended visceral organ injury, blood vessel damage, and inaccurate placement. An important principle is that surgeons should maintain strong familiarity with their system of choice to minimize risk of adverse outcomes during entry into the surgical space.

B. Port Placement

The general scheme of port placement is to surround the site with the necessary number of instruments placed widely enough apart that they do not "sword fight" in the abdomen and with the laparoscope situated so that a good visual angle can be attained.

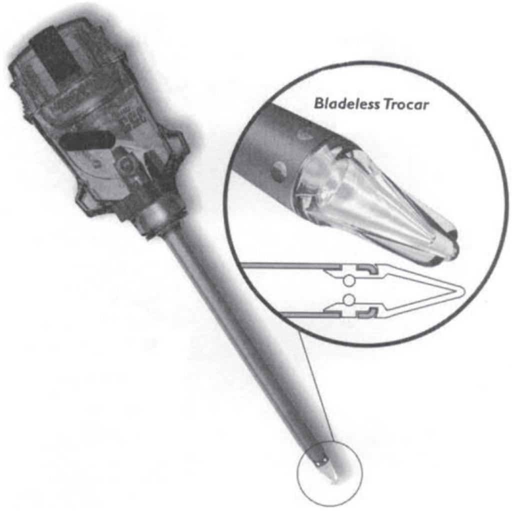
Standard port sizes range from 5 to 12 mm. "Needlescopic" ports (3 mm) as well as extrawide ports (18 and 30 mm) are available for specialized use. Ports can be disposable, reusable, or "reposable." The third contains both reusable and disposable components. The trocars inside the ports can be cutting or noncutting. Disposable sharp trocars are shielded (Figure 10–7). Some reusable trocars have nonshielded sharp



▲ **Figure 10–7.** Insertion of port with shielded sharp tip; a blunt shield moves forward to shield the blade once resistance decreases. (Used with permission from AutoSuture Co, Norwalk, CT.)

tips. The Hasson-type ports employ blunt tips. There are ports with clear plastic tips (Figure 10–8) that allow visualization with the laparoscope as the port is being inserted. The step system (AutoSuture, Norwalk, CT; see Figure 10–9) employs an expandable sheath that is inserted with a Veress needle. The needle is removed and a dilating trocar is used to insert the port. This and other ports that dilate or screw into the fascia ensure a smaller fascial defect and pose less risk of injury than sharp-tipped ports.

If the Veress needle has been used for abdominal entry, the next step is to place the first port, which is usually for the laparoscope and inserted at the site of Veress needle placement. To avoid inadvertent removal of the port during the procedure, anchor it to the skin with suture. Alternatively, special sheaths can secure the port. Subsequent ports are placed under visual control through the laparoscope.



▲ **Figure 10–8.** Nonbladed trocar, with clear plastic tip that allows visualization as the abdominal wall is penetrated. (Used with permission from Ethicon Endo-Surgery, Cincinnati, OH.)

C. Extraperitoneal Approach

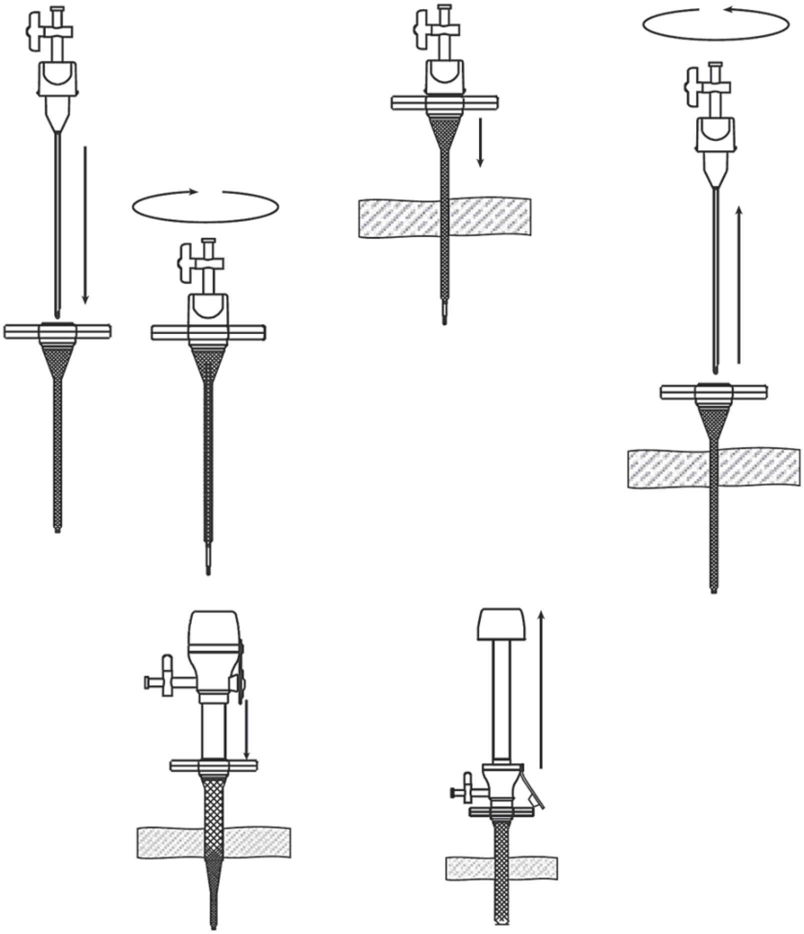
For flank retroperitoneoscopic surgery, make a 2-cm incision near the tip of the 12th rib down through the lumbodorsal fascia under direct vision. Explore the retroperitoneal space with a finger, and then dilate the space with a balloon (commercially available [Figure 10–10] or self-made). Insert a self-retaining port at this location, and place additional ports as needed. For pelvic extraperitoneal surgery, direct the balloon through an infraumbilical incision toward the pubic bone and dilate the preperitoneal space.

▶ Laparoscopic Video Instrumentation and Cart

The standard adult laparoscope is 10 mm in diameter, although the newer 5-mm laparoscopes provide excellent images, and many surgeons now use them routinely. For pediatric surgery, a 5-mm laparoscope typically is used, but 2-mm laparoscopes are also available. Most laparoscopes employ a 0° or 30° lens, with the latter providing more viewing angles, and laparoscopes with flexible tips are also available. In some laparoscopes, the camera chip is placed on the tip, which removes an interface and enhances resolution. One or two large monitors, a strong light source with cables in good condition, and the digital image converter (camera box) complete the video apparatus. Still-image and videocapture devices provide documentation. Other equipment on the laparoscopic cart includes the insufflator and additional energy sources.

▶ Laparoscopic Instrumentation

Laparoscopic operating instruments provide grasping and dissection, cutting, hemostasis, retraction, irrigation and aspiration, suturing, clipping or stapling, specimen entrapping,



▲ **Figure 10–9.** Step system port. (Used with permission from AutoSuture Co, Norwalk, CT.)

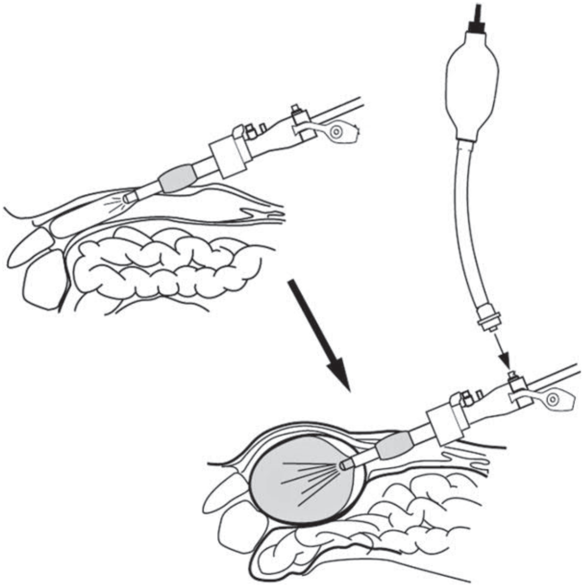
morcellating, and intraoperative imaging. Many are available in both disposable and reusable versions. Most standard instruments are 5 or 10 mm in diameter and 35 cm in length, but there are longer, narrow, or wider devices for specific uses.

Exiting the Abdomen

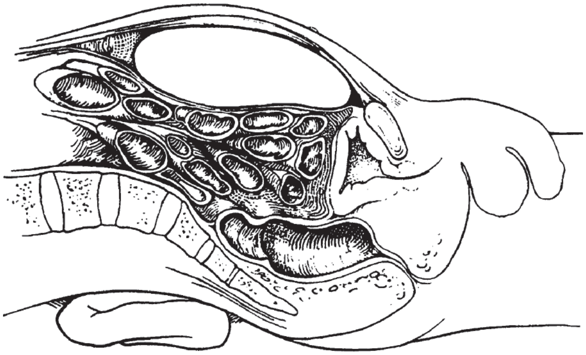
After a laparoscopic procedure is completed, inspect the operative field at 5 mm Hg pressure to allow exposure of bleeding that may have been tamponaded by the working pneumoperitoneum pressure. Remove the ports under vision so that any bleeding from the abdominal wall can be detected. Close the fascial defect of all port sites ≥10 mm. The Carter–Thomason needle suture passer (Figure 10–11) (Inlet Medical Inc., Eden Prairie, MN) or similar devices simplify this step. In children, close even 5-mm port sites. Because retained CO_2 may contribute to postoperative discomfort, attempt to remove all gas. Close the port incisions with a subcuticular stitch or wound glue and apply sterile tape.

Postoperative Care

For urologic laparoscopic procedures that do not involve bowel resection, hospital stay can be limited to 1 or 2 days in most patients with aggressive postoperative management. For major surgeries involving bowel resection such as radical cystectomy, enhanced recovery after surgery (ERAS) protocols that encourage rapid advancement of diet and early ambulation have proven to reduce length of hospital stay. It is not uncommon after laparoscopic surgery for patients to have some element of ileus for the first 24–48 hours following surgery. In the absence of predisposing factors for bowel dysfunction, in patients with sustained nausea or vomiting or inability to tolerate oral intake after surgery, suspicion for unrecognized bowel injury should be high.



▲ **Figure 10–10.** Preperitoneal distention balloon. (Used with permission from AutoSuture Co, Norwalk, CT.)



▲ **Figure 10–12.** Balloon device inflated in the preperitoneal space for extraperitoneal laparoscopic pelvic lymph node dissection.

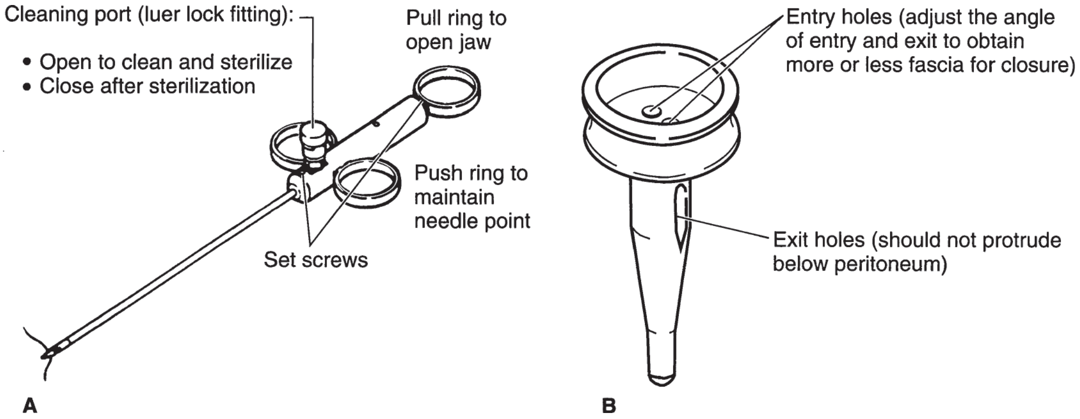
SPECIFIC PROCEDURES

Pelvic Lymph Node Dissection

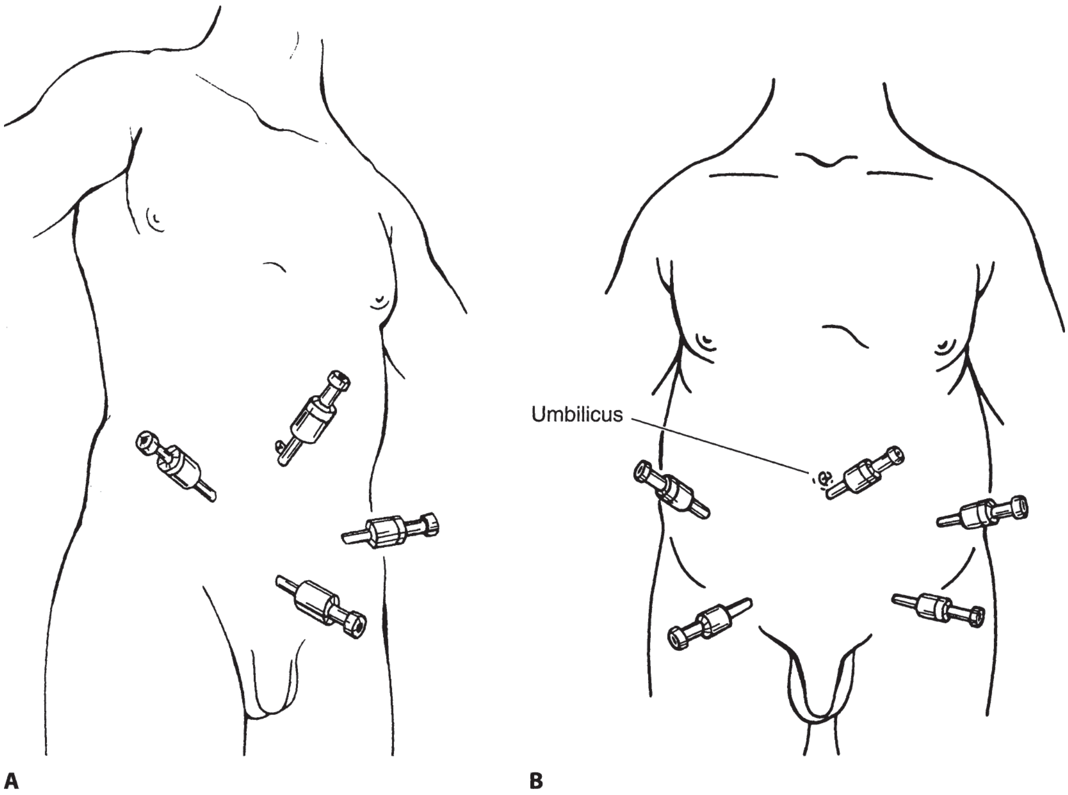
Laparoscopic pelvic lymph node dissection (LPLND) in the setting of prostate cancer was the first adult laparoscopic urologic procedure to gain widespread acceptance. The technique was initially described prior to widespread prostate-specific antigen testing, and LPLND had positive results in up to one-third of prostate cancer patients. Because of the lower positive node rates associated with stage migration, interest in standalone LPLND has waned. With the rise of laparoscopic/robotic radical prostatectomies and cystectomies, however, the utility of LPLND (as part of these procedures) remains.

There are no contraindications specific to LPLND other than those general to laparoscopy, although intraperitoneal laparoscopic hernia repair, other pelvic surgery, or radiotherapy can result in adhesions.

The patient is positioned supine with Trendelenburg tilt. LPLND can be performed transperitoneally or extraperitoneally (Figure 10–12). Initial access is typically through an umbilical port followed by two to three additional ports in a diamond- or fan-shaped pattern (Figure 10–13). Key landmarks are the obliterated umbilical ligament, gonadal vessels,


Cleaning port (luer lock fitting):
• Open to clean and sterilize
• Close after sterilization
Pull ring to open jaw
Push ring to maintain needle point
Set screws
A
Entry holes (adjust the angle of entry and exit to obtain more or less fascia for closure)
Exit holes (should not protrude below peritoneum)
B

▲ **Figure 10–11.** Carter–Thomason device. ***A:*** Needlepoint suture passer. ***B:*** Fascial closure guide. (Used with permission from Inlet Medical Inc., Eden Prairie, MN.)



▲ **Figure 10–13.** Port placements for laparoscopic pelvic lymph node dissection. ***A:*** Diamond configuration typically used. ***B:*** Fan configuration for use in obese patients.

and internal inguinal ring (Figure 10–14), with the limits of the nodal dissection for prostate cancer usually being the iliac bifurcation, the pubis, the obturator nerve, the pelvic side wall, and the medial umbilical ligament. Dissection for bladder, penile, or urethral cancer usually involves a more extended field, bounded by the common iliac artery, the genitofemoral nerve, and the bladder.

Complications of LPLND are similar to those of open PLND. Specifically, injuries to the obturator nerve, iliac and epigastric vessels, and ureter have been reported but are uncommon. Other potential complications include lymphocele, bowel or bladder injury, subcutaneous emphysema, thromboembolic events, and scrotal swelling. Open surgical pelvic lymphadenectomy and LPLND provide similar nodal yield.

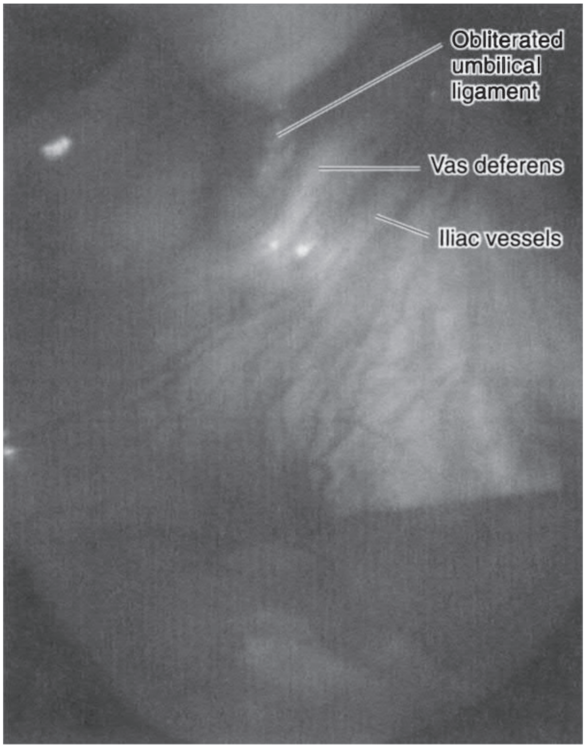
▶ Varicocelectomy

Laparoscopic varicocelectomy is performed less often today because of refinements in the subinguinal microsurgical technique (Ahmed et al, 2007). There have been small case series reporting use of two ports (Seo et al, 2018) for scarless laparoscopic varicocelectomy.

▶ Orchidopexy

Laparoscopy has been judged by many pediatric urologists to be the gold-standard diagnostic tool for nonpalpable testes. Although not as firmly established, laparoscopic orchidopexy appears to be comparable with, if not better than, open orchidopexy (Baker et al, 2001). Laparoscopy may be used for intersex evaluation as well (Tafazzoli et al, 2018).

Positioning is usually supine with the legs frog-legged. A small laparoscope is inserted through a periumbilical site. One to three port sites have been utilized. The first step involves identifying the inguinal ring with the corresponding gonadal vessels and vas deferens. If the vas deferens and vessels are seen entering the inguinal ring, the laparoscope is removed, and an open inguinal exploration is performed as would be for a palpable cryptorchid testis. If the gonadal vessels are blind-ending, the procedure is terminated. If an unsalvageable testis is identified, laparoscopic orchiectomy can be performed. If a salvageable testis is identified intra-abdominally, working ports are placed and the testis is freed from its nonvital attachments (Figure 10–15). If sufficient cord length can be gained, a scrotal incision is made and the



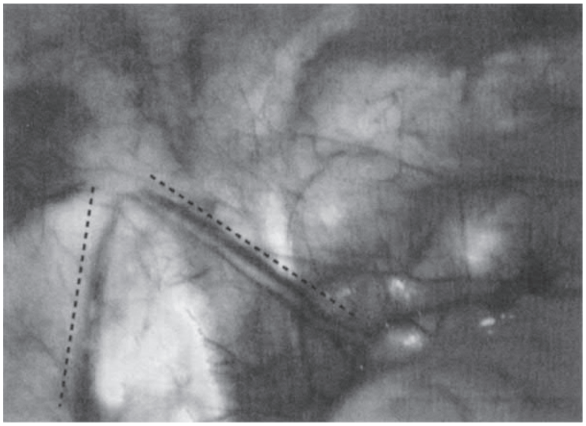
▲ **Figure 10–14.** Key landmarks for laparoscopic pelvic lymph node dissection are the obliterated umbilical ligament, gonadal vessels, and internal inguinal ring.

testis is fixed in a scrotal location. If there is insufficient cord length, a one- or two-stage Fowler–Stephens procedure may be performed. A multi-institutional review found decreased testicular atrophy and a higher rate of postoperative scrotal testicular positioning after the two-stage procedure. Some studies have shown increased success with an open approach for the second stage procedure rather than a laparoscopic approach (Casanova et al, 2013).

Renal Cyst Decortication

Although simple renal cysts are common, they rarely require intervention. Occasionally, pain, infection, early satiety, or secondary obstruction can develop that prompts active treatment, although in many cases, percutaneous aspiration and sclerosis of the cyst will suffice. Even less frequently, a cystic mass may need to be explored for diagnostic purposes. Cyst decortication also can be performed for pain relief in patients with polycystic kidney disease who still have adequate renal function.

Via a three- or four-port approach (usually transperitoneal), the colon is reflected medially to expose the kidney, and Gerota's fascia is incised to expose the cyst(s). Laparoscopic ultrasound may be useful. If there is suspicion of a connection to the collecting system, or if the collecting system is nearby and at risk for injury, instillation of dyed saline through a previously placed retrograde ureteral catheter may be useful. The roof of the cyst is excised, without incising into surrounding renal parenchyma. A biopsy of any suspicious areas should be obtained. Perirenal fat may be fixed to the cyst base to help prevent cyst reaccumulation (Lai et al, 2017). Long-term success is high (Yoder and Wolf, 2004). Complications specific to renal cyst decortication include cyst regrowth and injury of renal parenchyma or collecting system.



▲ **Figure 10–15.** *Dashed lines* indicate incisions into posterior peritoneum for orchidopexy of a left intra-abdominal testis.

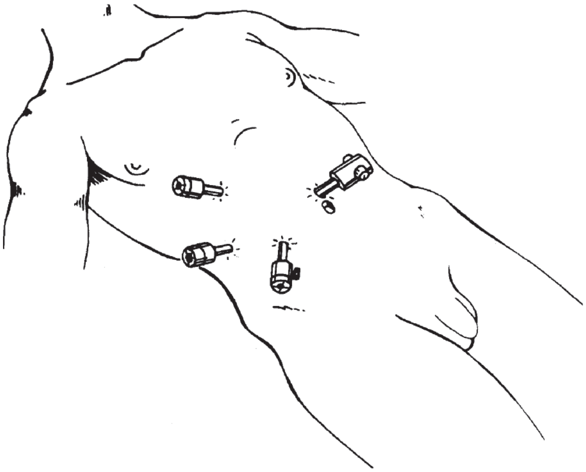
Simple and Radical Nephrectomy

Laparoscopy has become a well-accepted technique for numerous benign and malignant renal conditions, including nonfunctioning kidneys, chronic infections, symptomatic polycystic kidney disease, and tumors. Initially, large tumor size was considered a contraindication for laparoscopic nephrectomy, but with experience, tumor size has become less of an issue. The only limitation is the expertise of the urologist. Laparoscopic radical nephrectomy, including renal vein thrombus, is feasible. Relative contraindications include profound perirenal inflammation, bulky lymphadenopathy that limits hilar access, large venous thrombus, and adjacent-organ involvement.

The patient is placed in a lateral decubitus position, padded, and secured. Table flexion and variation in decubitus position ranging from 45° to 90° varies with the specific approach and surgeon preference. The surgeon and assistant both stand toward the patient's anterior body wall for the transperitoneal approach.

The techniques for a laparoscopic nephrectomy will be discussed in detail as a template for other common laparoscopic upper retroperitoneal procedures. There are many variations on port placement. For transperitoneal laparoscopic nephrectomy, a three- to four-port L-shaped configuration for left nephrectomy and a reversed L-shaped pattern for right nephrectomy are commonly used. The initial port is placed two fingerbreadths below the costal margin at the lateral edge of the rectus muscle and the abdomen is insufflated initially to 15–18 mm Hg. Intra-abdominal organs are inspected for inadvertent injury. Another port is placed in the midaxillary line two fingerbreadths above the iliac crest. One to two additional ports are placed along the lateral edge of the rectus muscle, including one able to accept the endoscopic stapler if use is anticipated. Depending on the patient's body habitus and relative position of the kidney and spleen/liver, other configurations may be chosen (Figure 10–16).

For left-sided lesions, the left colon is mobilized from the splenic flexure toward the iliac vessels, leaving the anterior fascicle of Gerota's fascia intact. The lienophrenic ligament is incised, allowing medial rotation of the spleen. Further medial rotation is achieved by mobilizing the lateral edge of the pancreas, thus revealing the renal hilum. The ureter is identified and transected. Following the gonadal vein superiorly will help identify the renal vein. The renal vein is dissected over the aorta to help avoid damage to the adrenal or lumbar veins. One should be careful using clips on vascular branches near the renal hilum because these can interfere with subsequent utilization of the endoscopic stapler. The renal artery is typically found posterior to the renal vein and is transected after securing it with clips or an endoscopic stapler. Once the artery is transected, the renal vein is secured and transected in a similar fashion. If the hilar dissection is difficult and the vein and artery cannot be separated, the endoscopic stapler can be used to transect the artery and vein en bloc. The superior border of the kidney is dissected, either incorporating the adrenal gland or more medially if adrenal sparing is intended. The lateral renal attachments are the last to be transected, because they help suspend the kidney and ease hilar dissection.

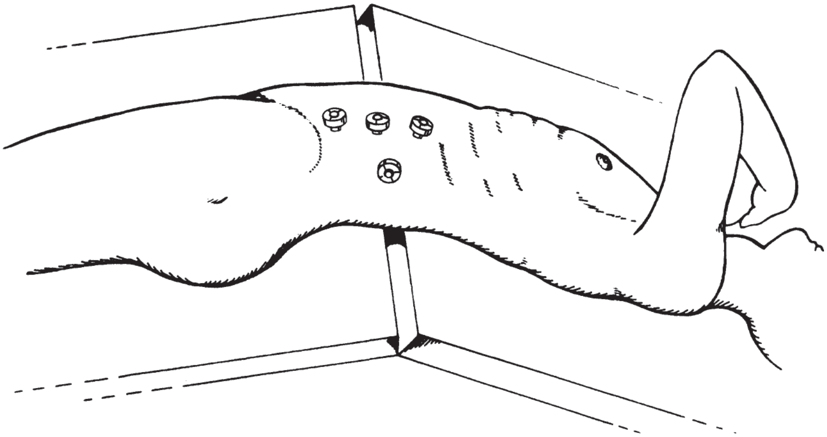


▲ **Figure 10–16.** One of the possible port configurations for right transperitoneal laparoscopic nephrectomy.

The kidney can be removed intact or morcellated after being placed into a specimen retrieval bag. If intact extraction is desired, a premarked incision is utilized, or a port site may be extended for extraction. For morcellation, the neck of the bag is brought through the port site. Appropriate drapings should be used to prevent potential tumor seeding. Blunt forceps are used to remove the specimen piecemeal, and laparoscopic monitoring is used to help prevent injuries. These instruments are then considered contaminated and are removed from the field. As with all laparoscopic procedures, insufflation pressures should be reduced to 5 mm Hg for final evaluation of hemostasis. Port sites > 5 mm that utilized cutting trocars require fascial closure.

For right-sided transperitoneal nephrectomy, the ascending colon is mobilized from the hepatic flexure toward the iliac bifurcation. The triangular ligament is incised, with caution to avoid injuring the diaphragm. The liver is retracted with a blunt-tipped instrument. The duodenum is mobilized medially to help expose the inferior vena cava (IVC). Entering the plane of Leriche directly anterior to the IVC will guide dissection to the renal vein. Dissection lateral to the lower edge of the IVC will reveal the psoas muscle and ureter. Although the right renal vein is shorter, it rarely has veins draining into it as on the left side. The remainder of the technique is similar to that described earlier.

Retroperitoneal nephrectomy begins with the patient in a full lateral decubitus position with similar padding and bed adjustments. In contrast to the transperitoneal approach, the surgeon and the assistant stand on the dorsal side of the patient. After an incision is made over Petit's triangle, blunt dissection through the lumbodorsal fascia is performed and a plane is developed over the psoas muscle. A dissecting balloon trocar is placed into this space. There are commercially available dissecting balloon trocars for this purpose, or a "homemade" version can be constructed by attaching a glove to a catheter. The commercially available dissecting trocar has the advantage of allowing direct visual monitoring of the dissection. Pneumoretroperitoneum is created, and two to three additional port sites are placed according to surgeon preference (Figure 10–17). The kidney is retracted anteriorly to allow direct access to the hilum. Blunt dissection easily exposes the artery, which is clipped and transected. Anterior to the arterial stump, the vein is dissected and controlled. After hilar control, the ureter is identified and transected. Further dissection is similar to that employed in transperitoneal procedures. Many laparoscopists remove the specimen intact when performing retroperitoneoscopic nephrectomy, due to the limited workspace. If morcellation is preferred, specimen-bag entrapment may require incising the peritoneum if the specimen is large. The final steps of ensuring hemostasis under low-pressure insufflation and inspecting the port sites remain the same.



▲ **Figure 10–17.** One of the possible port configurations for left retroperitoneal laparoscopic nephrectomy.

The technique for hand-assisted laparoscopic nephrectomy is similar to that employed for transperitoneal laparoscopic nephrectomy. If hand assistance is chosen, port placement is altered to allow room for the hand assistance device. For left-sided lesions, the hand assistance device is typically placed in the midline and may incorporate the umbilicus. For obese patients, the device may be placed paramedian, closer to the pathology. For right-sided lesions, the device may be placed in the midline or alternatively in the right lower quadrant using a muscle-splitting diagonal incision (Gibson). Placement of the hand assistance device is dependent on the surgeon's arm length, desired position of the nondominant hand, and the patient's body habitus. Two or three ports are placed according to surgeon preference. Dissection is similar to that employed in the transperitoneal procedure described earlier. Lateral renal attachments can be transected earlier because the hand can provide counter traction, facilitating hilar dissection. Specimen extraction is rapidly performed through the hand-assisted incision.

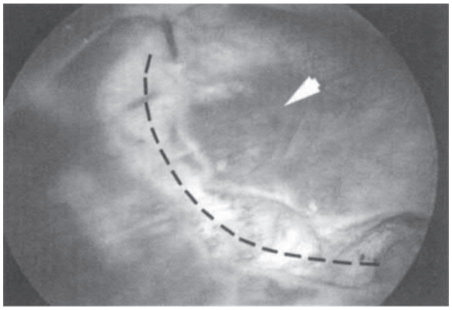
The major complication rates from laparoscopic nephrectomy are approximately 4%. Minor complications include ileus, mild hemorrhage, urinary tract infection, hernia, and wound infection. Major complications include pulmonary embolus, pneumothorax, injury to various viscera, and hemorrhage from the aorta, IVC, or iliac, gonadal, lumbar, or renal vessels. Technical complications are more common during the first 30–50 cases of a surgeon's experience.

Comparisons of laparoscopic and open surgical nephrectomy reveal shorter and less intense convalescence with laparoscopy and similar complication and cancer-control rates (Columbo et al, 2008). Operative times are longer for laparoscopy initially, but with experience, operative times may even be shorter than with open surgery. Studies comparing different laparoscopic techniques show similar outcomes, suggesting that no approach is uniformly superior (Gabr et al, 2009). The surgeon should be familiar with the various techniques so that the optimal procedure can be performed.

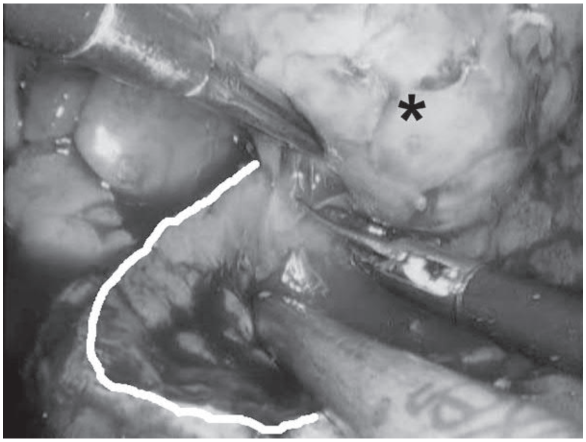
▶ Nephroureterectomy

Nephroureterectomy is the gold-standard treatment for upper tract urothelial carcinoma. The open surgical procedure is performed through a long, curved flank incision or two separate incisions, leading to significant postoperative morbidity. Laparoscopic nephroureterectomy incorporates the benefits of cancer control with less postoperative pain and earlier return to normal activity. Transperitoneal, retroperitoneal, hand-assisted, and robot-assisted techniques have been described. The kidney dissection is similar to a laparoscopic radical nephrectomy, except that the ureter is left intact prior to the distal transection.

Optimal management of the distal ureter remains controversial. The technique of transurethral resection of the intramural ureter, leaving the distal ureter–free in the retroperitoneum, has been largely abandoned, owing to risk of local recurrence. A number of alternative minimally invasive approaches have been described, including one- or two-port transvesical dissection of the distal ureter (Figure 10–18) with (two-port) or without (one-port) transvesical closure of the ureteral orifice, endoscopic stapling, or energy ablation of the tented-up ureter from an extravesical approach, and others. Some simply perform the nephrectomy laparoscopically and excise the bladder cuff and remove the specimen through a lower abdominal incision. Even in cases without open surgical bladder cuff, the nephroureterectomy specimen should always be removed intact. Cancer control rates appear to be adequate, and complication rates are similar to those for laparoscopic radical nephrectomy (Manabe et al, 2007; Liu et al, 2018), although patients with advanced disease may benefit from an open approach (Peyronnet et al, 2017).



▲ **Figure 10–18.** Transvesical dissection of the distal ureter performed with a Colling's knife on a resectoscope placed through a 10-mm port inserted suprapubically into the bladder. After the nephrectomy portion of the procedure and clipping of the ureter, incision (*dotted black line*) is gradually made around the ureteral orifice (*white arrowhead*) until the distal ureter can be pulled free of the bladder.



▲ **Figure 10–19.** Partial nephrectomy. Tumor (*black asterisk*) is being elevated by a grasper (entering from top of figure), as it is excised with scissors. An irrigator–aspirator depresses the tumor bed and helps maintain visualization. The peripheral resection margin is indicated with the *white line*.

Partial Nephrectomy and Renal Mass Ablation

Partial nephrectomy is performed for imperative, relative, and elective indications. Some patients who are candidates for open surgical partial nephrectomy have been treated inappropriately with laparoscopic radical nephrectomy because of the more favorable postoperative convalescence. The laparoscopic approach to partial nephrectomy, however, provides both nephron-sparing results and improved convalescence. Widespread adoption of the procedure has been limited by its technical difficulty.

Transperitoneal, retroperitoneal, hand-assisted, and robot-assisted techniques have been described. Although the overall technique is similar to that employed for laparoscopic radical nephrectomy, a few modifications are required. Some physicians perform preoperative ureteral catheterization to assess collecting system closure. Laparoscopic ultrasound may be useful to delineate tumor margins and multifocality. The kidney is dissected from perirenal fat as needed to expose the lesion (leaving a cap of fatty tissue over the tumor) and bring it into the operative field. The renal artery may be occluded with a laparoscopic bulldog or Satinsky clamp, or direct manual compression using hand assistance can be used. Superficial lesions can be excised without hilar clamping, and methods for "clampless" partial nephrectomy for deeper lesions have been reported. Parenchymal cooling using various methods has been described, but it is not standard, although other maneuvers to minimize reperfusion injury (intravenous fluids, mannitol, etc) are frequently used. Tumors are resected with "cold" scissors or energy devices (Figure 10–19). The use of biopsies and frozen section is variable. Vessels and collecting system entry sites are closed using intracorporeal suturing techniques and/or tissue glues. The overlying parenchyma is frequently coagulated using the laparoscopic argon-beam coagulator. Tissue glues and bulking agents (collagen, gelatin, etc) may be placed on the resection bed to help optimize hemostasis. Bolstering sutures can be placed to compress and reconstruct the remaining renal tissue.

Complications of laparoscopic partial nephrectomy include hemorrhage and urinary leak, generally at a rate somewhat greater than that for open surgical partial nephrectomy (Gill et al, 2007). Cancer control rates appear to be equivalent to those of open partial nephrectomy. In comparing laparoscopic, robotic, and open partial nephrectomy, a 2018 multicenter analysis found similar rates of local recurrence, distant metastasis, and cancer related death after 5-year median follow-up; however, robot-assisted partial nephrectomy was associated with a lower rate of chronic kidney disease upstaging (Chang et al, 2018).

An alternative to tumor resection is cryoablation or radiofrequency ablation of small peripheral renal lesions. The dissection techniques are similar to those employed for laparoscopic partial nephrectomy. A biopsy should be taken to confirm malignancy. For cryoablation, the probe is passed into the tumor and the lesion is frozen to less than −20°C, thawed, and then refrozen. This process can be monitored by laparoscopic ultrasound. For radiofrequency ablation, the probe is introduced into the lesion after adequate mobilization and biopsy and is used to deliver a preset amount of energy based on tumor volume. Temperature at the tip of the probe is 100°C. After treatment, the lesion may be resected, or the coagulated mass can be left in situ. Cryoablation and radiofrequency coagulation techniques may decrease blood loss and operative times compared with partial nephrectomy. Renal arterial clamping is unnecessary, thus avoiding the risk of ischemia and reperfusion injury. The spectrum of complications is similar to that found for laparoscopic partial nephrectomy. Long-term data are scant, and close follow-up is required (Kunkle and Uzzo, 2008). Meta-analysis shows a slightly higher rate of local recurrence-free survival for partial nephrectomy relative to thermal ablation; however, after multiple ablations, this difference was not found to be significant (Pierorazio et al, 2016).

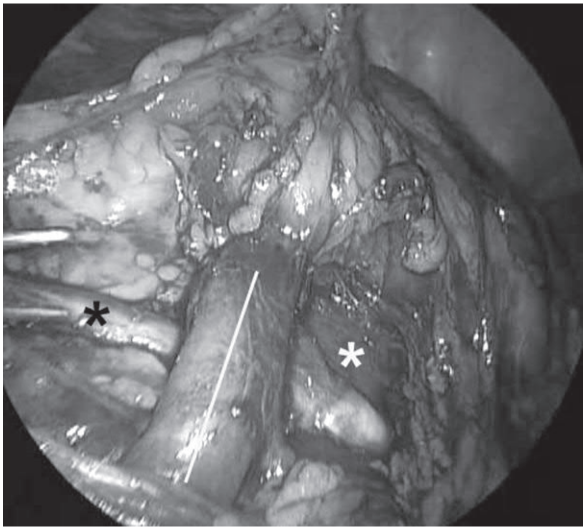
Donor Nephrectomy

Laparoscopy has become the standard for donor nephrectomy in the United States. Most laparoscopic procedures are left-sided, single-artery kidneys for technical reasons, but multiple arteries and right-sided donation can be addressed with excellent outcomes. The positioning and dissection technique is similar to that of laparoscopic nephrectomy, except that the ligation of the vasculature is the last step before intact extraction. For the pure laparoscopic technique, a premarked low transverse incision is carried down to the peritoneum. The renal artery and vein are then ligated and transected. To optimize renal vein length, especially on the right side, an endoscopic stapler that lays down three rows of staples without cutting can be used, in place of the more commonly used stapler that lays down six rows of staples and cuts in between rows 3 and 4. A peritoneotomy is made, and the kidney is passed to the recipient team.

Many centers use hand-assisted laparoscopic techniques for live renal donation. Hand-assisted laparoscopic donor nephrectomy has been associated with slightly shorter ischemia time and operative time relative to pure laparoscopic donor nephrectomy (Broe et al, 2018). Proponents of hand-assisted approaches argue that the incision should be made at the beginning of the procedure and utilized for assistance in dissection. Others use the retroperitoneal approach for laparoscopic donor nephrectomy, claiming decreased operative times. Surgeon experience and comfort level will dictate the laparoscopic technique. Laparoscopic donor nephrectomy produces renal units that function as well as those from open surgical procedures, with similar complication rates (Nanidis et al, 2008).

Pyeloplasty

Laparoscopic pyeloplasty is increasingly utilized to address ureteropelvic junction obstruction. Transperitoneal, retroperitoneal, and hand-assisted techniques have been described. Common to all approaches is the need to be well skilled in laparoscopic suturing, and as such robotic assistance has become popular. Port placement is similar to that utilized for laparoscopic transperitoneal or retroperitoneal nephrectomy. Dissection and reconfiguration of the ureteropelvic junction are similar to those for open surgery and are dependent on intraoperative findings. The Anderson–Hynes dismembered pyeloplasty, Y-V plasty, Heineke–Mikulicz reconstruction, Davis intubated ureterotomy, Hellstrom vascular relocation, and tubularized flap pyeloplasty have all been described with reference to laparoscopy. The procedure has been performed in infants, children, adults, and the elderly. If there is an anterior crossing vessel, it is optimal to transect and anastomose the ureter anterior to the crossing vessel (Figure 10–20). A large redundant renal pelvis may be reduced and tapered. A ureteral stent may be placed before or during the repair.



▲ **Figure 10–20.** Ureteropelvic junction obstruction of left kidney associated with crossing vessel (*white line*) before laparoscopic pyeloplasty. Renal pelvis is marked with *white asterisk*; ureter is indicated by a *black asterisk*.

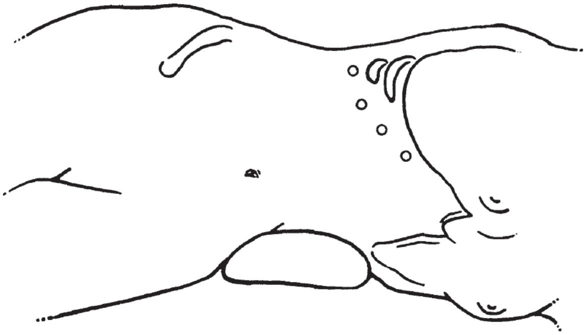
Open surgical and laparoscopic pyeloplasty appear to offer equivalent pain relief, activity-level improvement, and relief of obstruction. The outcomes are better than with other minimally invasive approaches such as endopyelotomy or balloon dilation (Dimarco et al, 2006). In pediatric patients robotic pyeloplasty is gaining traction with reduction in complication rates but high cost (Chang et al, 2015). Complications are similar to those for laparoscopic nephrectomy, with the addition of urinary leak and failure of the procedure to correct the obstruction.

Adrenalectomy

On the basis of shorter operative time, reduced complications and convalescence, and equivalent surgical outcome compared with open surgery, laparoscopic adrenalectomy is the standard approach for most surgical adrenal lesions, including aldosteronomas, pheochromocytomas, Cushing's adenomas, incidentalomas, metastatic lesions, symptomatic myelolipomas, and feminizing/virilizing tumors (Lee et al, 2008). Experienced laparoscopists have reported successful laparoscopic adrenalectomy for ≤15-cm lesions. Transperitoneal (anterior or lateral), retroperitoneal (posterior or lateral), hand-assisted, and transthoracic laparoscopic approaches have been reported. Bilateral synchronous adrenalectomy and partial adrenalectomy have been performed.

The laparoscopic approach to the adrenal gland is similar to the approach described previously for transperitoneal laparoscopic nephrectomy, although the ports are placed in a subcostal location (Figure 10–21). The dissection can be compared to opening a book. For left-sided lesions, the spleen is mobilized medially, while the characteristic yellow adrenal tissue is mobilized to the right. Dissection continues in a counterclockwise direction. The main adrenal vein enters the renal vein. Proceed cautiously at the superomedial aspect because the superior adrenal vein (from the inferior phrenic vein) can be substantial. After controlling the adrenal vein, blunt and sharp dissection is used to mobilize the adrenal gland from the psoas muscle and superior aspect of the kidney. On the right side, the surgical approach is again analogous to opening a book, and dissection proceeds in a clockwise direction. The triangular ligament is incised with the posterior peritoneum, allowing medial retraction of the liver and colon. This exposes the IVC, and the adrenal gland is gently mobilized laterally. The adrenal vein emptying into the IVC is ligated and transected.

Major complication rate and length of hospital stay for robotic adrenalectomy are less than for laparoscopic adrenalectomy (Brandao et al, 2014). Vascular and visceral injuries, cardiovascular complications related to pheochromocytoma, pneumothorax, and other typical complications have been reported (Permpongkosol et al, 2005). Suppression of contralateral adrenal function by a cortisol-producing tumor (Cushing's syndrome) may result in an Addisonian crisis, typically within the first 10 postoperative days.

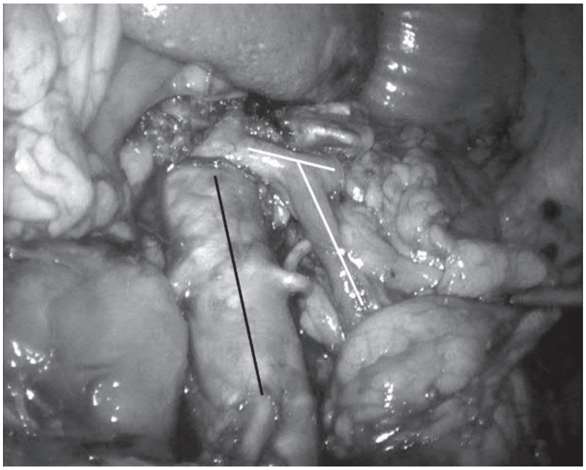


▲ **Figure 10–21.** One of the possible port configurations for right transperitoneal laparoscopic adrenalectomy.

Retroperitoneal Lymph Node Dissection

Open surgical retroperitoneal lymph node dissection (RPLND) involves a xiphoid-to-pubis midline incision and significant morbidity related to ileus, blood loss, and postoperative pain. Laparoscopic RPLND offer a considerably less intense experience for the patient. The dissection template is the same as with the open approach. For left-sided lesions, the para-aortic, preaortic, and retroaortic nodes are removed (Figure 10–22). The boundaries are the renal vessels, the medial edge of the aorta, and the ureter inferiorly down to the iliac vessels. For right-sided lesions, the interaortocaval, precaval, retrocaval, and preaortic nodes are removed. The boundaries are the renal vessels, the aorta, and the ureter inferiorly down to the iliac vessels. Additionally, the para-aortic nodes between the renal hilum and the inferior mesenteric artery are removed. Laparoscopic RPLND should be approached with caution in patients with bulky nodal disease.

The patient is positioned in a modified lateral decubitus fashion. The initial port is placed near the umbilicus. Additional ports are placed to optimize dissection and retraction. The dissection is similar to the previously described transperitoneal laparoscopic nephrectomy except that on the left side, the spleen and pancreas are rotated further medially, and the descending colon is mobilized lower into the pelvis. On the right side, the posterior peritoneum is incised under the liver to reveal the superior margin of the IVC, and the colon and duodenum are mobilized further medially to expose the retroperitoneal area of interest. A methodical approach, using the same split-and-roll technique as in open RPLND, is performed. Nerve-sparing techniques are similar to the techniques employed in the open approach, in hopes of preserving ejaculatory function.



▲ **Figure 10–22.** Left-sided laparoscopic retroperitoneal lymph node dissection. *Black line* indicates aorta; *white lines* indicate renal and gonadal veins.

Complications of laparoscopic RPLND include hemorrhage, lymphocele, chylous ascites, injury to renal and lumbar veins, and bowel injury. Postchemotherapy dissections are more difficult, with higher morbidity and conversion rates. Follow-up studies suggest oncologic efficacy comparable to that of open techniques (Rassweiler et al, 2008). Some centers have shown robotic RPLND to have outcomes comparable to those obtained with both open and laparoscopic approaches (Pearce et al, 2017).

▶ Radical Prostatectomy

Interest in laparoscopic urologic surgery intensified with successful laparoscopic techniques for radical prostatectomy. Laparoscopic prostatectomy has become routine in most centers with the availability of robotic assistance, with operative times similar to those needed for open prostatectomy. The indications for laparoscopic radical prostatectomy are similar to those of the open approach, and contraindications are the same as those for general laparoscopy.

A transperitoneal approach is most popular. The patient is positioned in a modified lithotomy fashion with the thighs abducted for access to the perineum and the table in steep Trendelenburg position. A periumbilical insufflation port is placed with four to five additional ports in a fan-shaped pattern. Laparoscopic dissection begins by incising the peritoneum posterior to the bladder to expose the seminal vesicles and vas deferentia, or by incising the peritoneum anterior to the bladder to open the space of Retzius. One major difference from the open procedure is that dissection of the prostate is often performed from the bladder neck distally to the prostatic apex. The lateral pedicles can be controlled with electrocautery or coagulating shears, or if nerve sparing is desired, then clips are used. The laparoscopic approach has the advantage of performing the anastomosis under magnified vision (and in three dimensions with the robot).

Once adequate experience has been gained, oncologic results (as measured by margins and prostate-specific antigen recurrence) are comparable with those with open radical prostatectomy (Ficarra et al, 2009). Similarly, incontinence and sexual dysfunction rates are comparable. Blood loss is less than that with open techniques, which is supposedly attributable to pneumoperitoneum helping to reduce venous hemorrhage and to improved and magnified visualization of vascular structures in the pelvis. Conversion to open surgery is rare after the initial learning curve.

▶ Radical Cystectomy with Urinary Diversion

The laparoscopic approach to radical cystectomy with urinary diversion, although growing in popularity, has not achieved the same dominance as in prostatectomy. The cystectomy portion of the procedure is often considered less technically demanding than prostatectomy; it is the urinary diversion with bowel that makes the procedure so difficult.

The cystectomy/cystoprostatectomy portion of the procedure is similar to that of laparoscopic radical prostatectomy. The urinary diversion with bowel can be performed through a "minilaparotomy" after first harvesting the bowel laparoscopically, or it can be performed totally intracorporeally. Data on oncologic efficacy and complications are still being obtained (Nix et al, 2010). Robot-assisted laparoscopic radical cystectomy is associated with lower blood loss and wound complications but can require a longer operative time relative to open radical cystectomy (Tan et al, 2016).

▶ Miscellaneous Laparoscopic Procedures

Numerous other laparoscopic procedures have been described. Interesting examples include laparoscopic ureteroneocystostomy for vesicoureteral reflux, psoas hitch with or without a Boari flap, augmentation enterocystoplasty, parapelvic cyst resection, lumbar sympathectomy, ileal ureter, anatrophic nephrolithotomy, pyelolithotomy, ureterolithotomy, flank herniorrhaphy, and catheterizable cecal tubes (ACE Malone). Continued improvement in technology, surgical skills, and patient demand will likely further expand laparoscopic urologic surgery.

COMPLICATIONS

During the first decade of urologic laparoscopy, its "steep learning curve" attracted much attention, Reports from pioneering centers indicated complication rates that were high initially but then fell markedly with experience (Kumar and Gill, 2006). For surgeons with laparoscopic experience during training, however, this "learning curve" is less dramatic (Cadeddu et al, 2001). In general, the rates of minor and major complications of laparoscopy are similar to those observed in open surgery. The intraoperative complications that are most feared during laparoscopy, just as in open surgery, are vascular and viscus injury. The problem with laparoscopy is that such injuries may require an emergent change in the approach (ie, conversion to hand assistance or open surgery), whereas in open surgery, the problem can be managed right there in the operating theater. As such, maneuvers during laparoscopic surgery must be more deliberate and careful, not because complications are easier to create but because they may be more difficult to manage.

FUTURE PERSPECTIVES OF LAPAROSCOPY

Laparoscopy is now well established in urology, although for some applications, laparoscopy has not yet reached its fullest potential. Evolving technologies likely will enhance not only laparoscopy but also all surgical endeavors. Laparoendoscopic single-site surgery, natural-orifice transluminal endoscopic surgery, microlaparoscopy, and robotic assistance continue to develop. The greatest challenge is to integrate laparoscopy into urologic practice such that it is a technique not only for specialists but also for all urologists with a surgical practice.

BIBLIOGRAPHY

Ahmed MA et al: Comparison of outcomes of different varicocelectomy techniques: Open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy: A randomized clinical trial. Urology 2007;69(3):417–420.

Azhar RA et al: Enhanced recovery after urological surgery: A contemporary systematic review of outcomes, key elements, and research needs. Eur Urol 2016;70(1):176–187.

Baker LA et al: A multi-institutional analysis of laparoscopic orchidopexy. BJU Int 2001;87(6):484–489.

Brandao L et al: Robotic versus laparoscopic adrenalectomy: A systematic review and meta-analysis. Eur Urol 2014;65(6):1154–1161.

Breda A et al: Association of bowel rest and ketorolac analgesia with short hospital stay after laparoscopic donor nephrectomy. Urology 2007;69(5):828–831.

Broe M et al: Laparoscopic and hand-assisted laparoscopic donor nephrectomy: A systematic review and meta-analysis. Arab J Urol 2018;16(3):322–334.

Cadeddu JA et al: Complications of laparoscopic procedures after concentrated training in urologic laparoscopy. J Urol 2001;166:2109–2111.

Casanova NC et al: Two-step Fowler-Stephens orchiopexy for intra-abdominal testes: A 28-year single institution experience. J Urol 2013;190(4):1371–1376.

Chang K et al: Functional and oncological outcomes of open, laparoscopic and robot-assisted partial nephrectomy: A multicentre comparative matched-pair analyses with a median of 5 years. BJU Int 2018.

Chang S-J et al: Comparing the efficacy and safety between robotic-assisted versus open pyeloplasty in children: A systemic review and meta-analysis. World J Urol 2015;33(11):1855–1865.

Columbo JR et al: Seven years after laparoscopic radical nephrectomy: Oncologic and renal functional outcomes. Urology 2008;71(6):1149–1154.

Desai MM et al: Prospective randomized comparison of transperitoneal versus retroperitoneal laparoscopic radical nephrectomy. J Urol 2005;173:38–41.

Dimarco DS et al: Long-term success of antegrade endopyelotomy compared with pyeloplasty at a single institution. J Endourol 2006;20:707–712.

Ficarra V et al: Retropubic, laparoscopic, and robot-assisted radical prostatectomy: A systematic review and cumulative analysis of comparative studies. Eur Urol 2009;55(5):1037–1063.

Forrest J et al: AUA Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. J Urol 2009;181(3):1170–1177.

Gabr AH et al: Approach and specimen handling do not influence oncological perioperative and long-term outcomes after laparoscopic radical nephrectomy. J Urol 2009;182(3):874–880.

Gill IS et al: Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007;178(1):41–46.

Hughes D, Camp C, O'Hara J, Adshead J: Health resource use after robot-assisted surgery vs open and conventional laparoscopic techniques in oncology: Analysis of English secondary care data for radical prostatectomy and partial nephrectomy. BJU Int 2016;117(6):940–947 (doi: 10.1111/bju.13401).

Junghans T et al: Effect of increasing cardiac preload, sympathetic antagonism, or vasodilation on visceral blood flow during pneumoperitoneum. Langenbecks Arch Surg 2005;390(6):538–543.

Kim YS: Arterial and end-tidal carbon dioxide pressure differences during laparoscopic colorectal surgery. Eur J Anaesthesiol 2008;25(1):74–75.

Kommu SS et al: Laparo-endoscopic single-site surgery: Preliminary advances in renal surgery. BJU Int 2009;103(8):1034–1037.

Kumar U, Gill IS: Learning curve in human laparoscopic surgery. Curr Urol Rep 2006;7(2):120–124.

Kunkle DA, Uzzo RG: Cryoablation or radiofrequency ablation of the small renal mass. Cancer 2008;113(10):2671–2680.

Lai S et al: The efficacy of retroperitoneal laparoscopic deroofing of simple renal cyst with perirenal fat tissue wadding technique: A retrospective study. Medicine 2017;96(41):e8259.

Lee J et al: Open and laparoscopic adrenalectomy: Analysis of the national surgical quality improvement program. J Am Coll Surg 2008;206(5):953–959.

Liu F et al: Laparoscopic versus open nephroureterectomy for upper urinary tract urothelial carcinoma: A systematic review and meta-analysis. Medicine 2018;97(35):e11954.

Manabe D et al: Comparative study of oncologic outcome of laparoscopic nephroureterectomy and standard nephroureterectomy for upper urinary tract transitional cell carcinoma. Urology 2007;69(3):457–461.

Min SK et al: Carbon dioxide and argon gas embolism during laparoscopic hepatic resection. Acta Anaesthesiol Scand 2007;51(7):949–953.

Montgomery JS, Wolf JS Jr: Venous thrombosis prophylaxis for urological laparoscopy: Fractionated heparin versus sequential compression devices. J Urol 2005;173(5):1623–1626.

Msezane LP et al: Case report: conservative management of a large capnothorax following laparoscopic renal surgery. J Endourol 2007;21(12):1445–1447.

Nanidis TG et al: Laparoscopic versus open live donor nephrectomy in renal transplantation: A meta-analysis. Ann Surg 2008;247(1):58–70

Nelson JB: Debate: Open radical prostatectomy vs. laparoscopic vs. robotic. Urol Oncol 2007;25(6):490–493.

Nix J et al: Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: Perioperative and pathologic results. Eur Urol 2010;57(2):196–201.

Ost MC et al: Urological laparoscopy: Basic physiological considerations and immunological consequences. J Urol 2005;174(4, pt 1):1183–1188.

Pearce S et al: Safety and early oncologic effectiveness of primary robotic retroperitoneal lymph node dissection for nonseminomatous germ cell testicular cancer. Eur Urol 2017;71(3):476–482.

Permpongkosol S et al: Complications of 2,775 urological laparoscopic procedures: 1993 to 2005. J Urol 2007;177(2):580–585.

Peyronnet B et al: Oncological outcomes of laparoscopic nephroureterectomy versus open radical nephroureterectomy for upper tract urothelial carcinoma: A European Association of Urology guidelines systematic review. Eur Urol Focus 2017.

Pierorazio P et al: Management of renal masses and localized renal cancer: Systematic review and meta-analysis. J Urol 2016;196(4):989–999.

Raman JD et al: Single-incision laparoscopic surgery: Initial urological experience and comparison with natural-orifice transluminal endoscopic surgery. BJU Int 2008;101(12):1493–1496.

Rassweiler JJ et al: Laparoscopic retroperitoneal lymph node dissection: Does it still have a role in the management of clinical stage I nonseminomatous testis cancer? A European perspective. Eur Urol 2008;54(5):1004–1019.

Saggar VR et al: Factors influencing development of subcutaneous carbon dioxide emphysema in laparoscopic totally extraperitoneal inguinal hernia repair. J Laparoendosc Adv Surg Tech A 2008;18(2):213–216.

Seo W et al: Laparoscopic 2-port varicocelectomy with scarless periumblical mini-incision: Initial experience in approach and outcomes. Urol J 2018;15(2):10–15.

Silberstein J, Parsons JK: Hand-assisted and total laparoscopic nephrectomy: A comparison. J Soc Laparoendosc Surg 2009;13: 36–43.

Tafazzoli K et al: Endoscopy and laparoscopy in disorders of sex development. Sex Devel 2018;12(1–3):100–105.

Tan W et al: Robotic assisted radical cystectomy with extracorporeal urinary diversion does not show a benefit over open radical cystectomy: A systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2016(11):e0166221.

Valentin MD et al: Recurrent asystolic cardiac arrest and laparoscopic cholecystectomy: A case report and review of the literature. J Soc Laparoendosc Surg 2004;8(1):65–68.

Wolf JS Jr: Devices for hand-assisted laparoscopic surgery. Expert Rev Med Devices 2005;2(6):725–730.

Yoder BM, Wolf JS Jr: Long-term outcome of laparoscopic decortication of peripheral and peripelvic renal and adrenal cysts. J Urol 2004;171(2):583–587.

Robotic Surgery in Urology

11

Maxwell V. Meng, MD, MPH

Minimally invasive surgery has played an important role in urologic surgery, with the widespread and frequent application of extracorporeal (shockwave lithotripsy), endoscopic, and laparoscopic techniques. Over the past decade, the introduction of robotic assistance has significantly altered the landscape of laparoscopic surgery in urology and will likely continue to play an important role in the future.

BACKGROUND

History

Despite the variety and complexity of operations achievable with traditional laparoscopy, major limitations included the two-dimensional vision and instrumentation with restricted degrees of freedom as well as reduced tactile feedback (haptics). Thus, initial efforts were limited to extirpative or ablative procedures, while technically demanding reconstruction requiring suturing and intracorporeal knot tying was limited primarily to highly experienced or specialized surgeons.

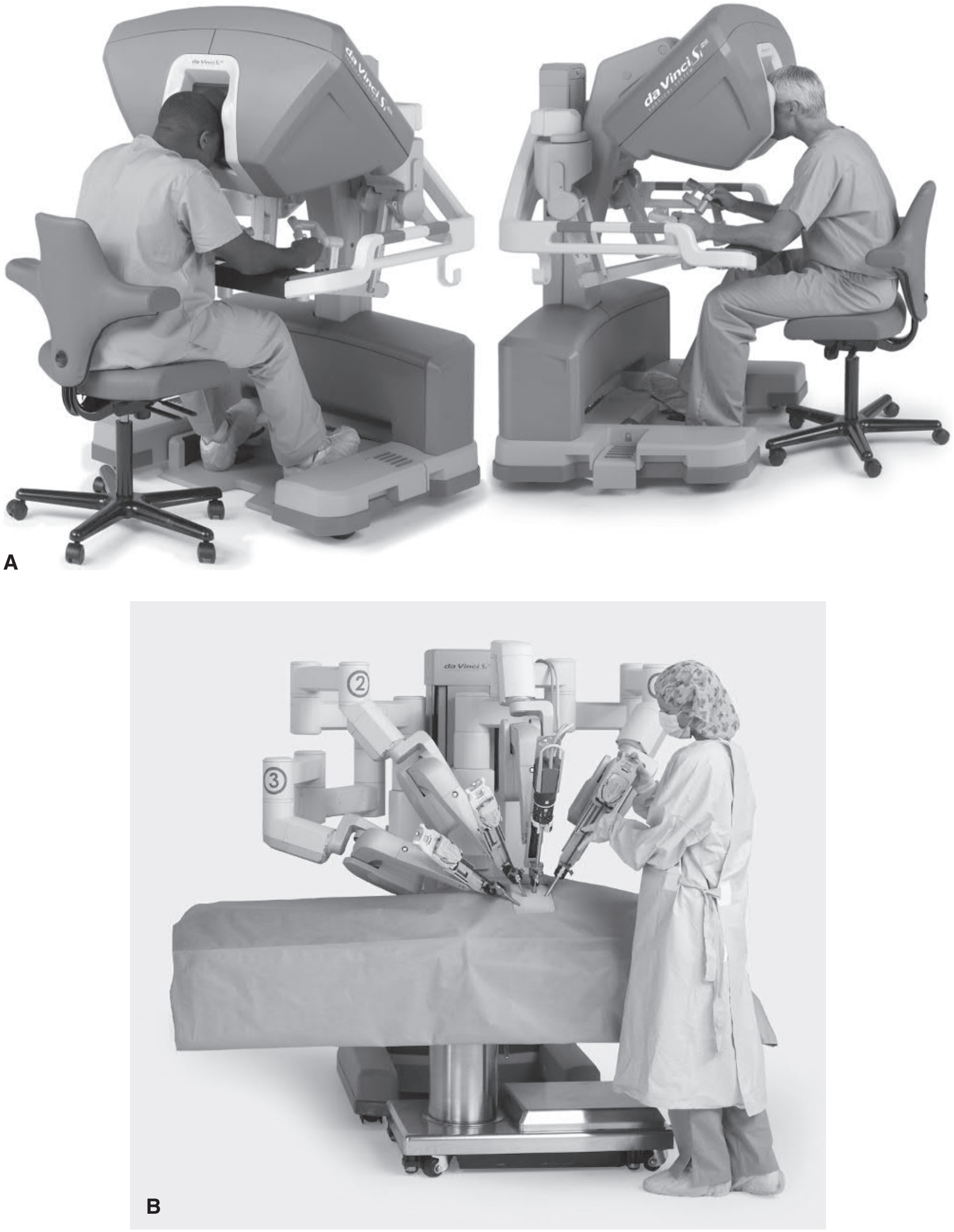
The concept of having an apparatus to aid or augment what is possible with the human hand is not new. The term **robot** is derived from the Czech word *robota*, meaning "work" or "forced labor," and was introduced by the writer Karel Capek. Isaac Asimov coined the term robotics, although the definition of a robot is quite varied. Critical elements of a robot include programmability, flexibility, and ability to interact with the environment. Thus, most robots are computerized systems with mechanical capabilities.

With respect to surgical robots, there are those that are shared control (robot is primarily an assistant, such as a camera holder), telesurgically controlled, and supervisor-controlled. The first robot utilized in urology was the PROBOT, an example of the last type where the robot performed transurethral resection of the prostate based on directions programmed into the controlling computer. The currently used robots are telesurgical primary—secondary systems, wherein the surgeon controls the robotic arms during the procedure from a remote console and the robot is merely an instrument; thus, given the lack of automation, procedures performed with these machines may be better categorized as robotic-assisted surgery.

Computer Motion Inc. developed both AESOP (automated endoscopic system for optional positioning), which controlled the endoscope using either voice or hand/foot control, and the ZEUS surgical system, consisting of three robotic arms attached to the operating table controlled remotely by the surgeon. In 2003, the company was acquired by Intuitive Surgical Inc., which was founded in 1995 and had developed the da Vinci surgical system, composed of a surgeon console, video tower and computer, and patient-side cart with three or four robotic arms.

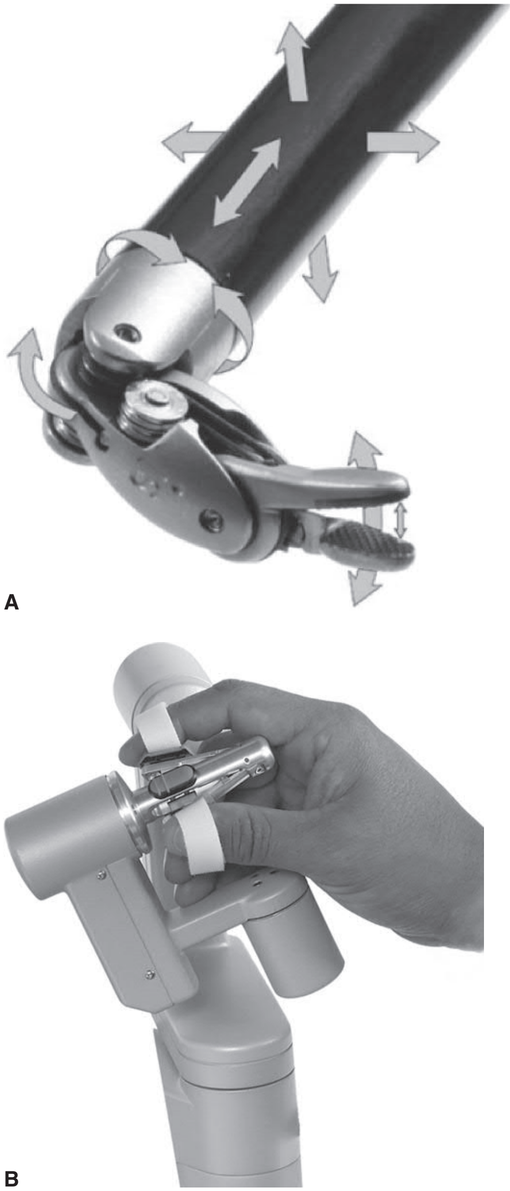
da Vinci System

Figure 11–1 shows the da Vinci system. It is currently the most widely utilized surgical robot with approximately 5000 units in operation worldwide. The surgeon sits at the console, where an immersive, three-dimensional view of the surgical field is provided. Control of the instruments is achieved via free-moving finger controls, which translate the physical motion of the fingers and wrists into electrical signals and computerized such that the robotic arms mirror these movements (Figure 11–2). The surgical cart consists of three or four arms, depending on the generation. True binocular vision is provided by an 8–12-mm endoscope with two separate video channels. A variety of interchangeable instruments are available and attached to the robotic arms, which are introduced into the body through 8- or 5-mm ports. The ends of the instruments have seven degrees of freedom and can mimic the surgeon's hand after tremor filtration and motion scaling, if desired.



▲ **Figure 11–1.** The da Vinci Si robotic surgical system made by Intuitive Surgical Inc. It consists of the ***(A)*** surgeon console (here with the dual console HD Si) and ***(B)*** patient-side surgical cart, in this model with four arms. (Used with permission from Intuitive Surgical Inc.).

Unlike traditional laparoscopy, the da Vinci system incorporates (1) three-dimensional vision, (2) articulation of the instruments at the wrist, (3) improved surgeon ergonomics, and (4) natural translation of surgeon movements to instrument tips. It remains to be determined whether incorporation of robotics into traditional urologic procedures improves patient outcomes, but for most surgeons, complex and reconstructive tasks are likely facilitated



▲ **Figure 11–2.** Example of the ***(A)*** EndoWrist technology, with seven degrees of freedom at the tip of the instrument and ***(B)*** surgeon's hand control at the console.

by robotic assistance. Although nearly every imaginable urologic operation, ranging from vasovasostomy to renal transplantation, has been performed with the aid of the robot, the remainder of the chapter discusses the most common and well-established applications of robotic surgery within urology.

LOWER URINARY TRACT OPERATIONS

Radical Prostatectomy

The initial target market for the da Vinci system was cardiothoracic surgery, attempting to minimize morbidity by avoiding a sternotomy and taking advantage of the precision and fine-instrument movement afforded by the robot. Both coronary revascularization and mitral valve repair are currently performed with robotic assistance, but the operations are technically demanding and have not expanded as rapidly as the application to radical prostatectomy. The first laparoscopic radical prostatectomy was performed in 1991, and several centers reported their experiences with the minimally invasive approach in the late 1990s. Despite refinements in techniques and outcomes comparable with those of traditional open prostatectomy, laparoscopic radical prostatectomy remained a challenging operation, with a significant learning curve, and was performed by relatively few surgeons. However, the operation ultimately proved to be the ideal application of robotic assistance, and over the past decade, it has largely supplanted both open and laparoscopic prostatectomy; by 2019 it is estimated that over 85% of radical prostatectomy operations in the United States will be performed with robotic assistance. Moreover, the robot is widely available and has been rapidly adopted by surgeons throughout the country, in both community and academic medical centers.

The operation is fundamentally no different from open or laparoscopic radical prostatectomy, with the goals of complete removal of the prostate and seminal vesicles, performing lymphadenectomy when indicated, and preservation of urinary and sexual function. Various approaches have been described, including transperitoneal versus extraperitoneal, and for the transperitoneal technique, the initial dissection can proceed either anteriorly (ie, retropubic space and through the bladder neck) or posteriorly (ie, dissection of the seminal vesicles and through the plane between the prostate and the rectum). Regardless of technique, the patient must be placed in a steep Trendelenburg position in order to displace the bowels cranially, away from the pelvis. Some patients with underlying cardiac or pulmonary disease or obesity may not tolerate being in this position for a prolonged period. In addition, the abdomen is insufflated with carbon dioxide typically to 15 mm Hg pressure, further affecting pulmonary and cardiac function and requiring careful monitoring by the anesthesia team. Meticulous attention to patient positioning is critical to prevent neuropraxia in the dark operating room environment; it may also be difficult to assess the patient with the additional equipment and bulk of the robotic system. Once the robot is docked in position with the camera and instruments inserted through the ports, the patient and operating room table cannot be moved until the instruments and robot are disengaged. Factors that make the robotic approach challenging include prior complex abdominal or pelvic surgery, morbid obesity, large prostate or median lobe, and prior radiation or prostate surgery; nevertheless, these are not absolute contraindications and surgery is often feasible despite these factors.

In assessing the success of robotic-assisted laparoscopic radical prostatectomy, the relevant outcomes of cancer control, urinary continence, and sexual function must be evaluated. Compared with open retropubic prostatectomy, robot-assisted prostatectomy is associated with decreased risks of operative blood loss and need for transfusion.

With respect to oncologic outcomes, open radical retropubic prostatectomy is the gold standard against which new techniques must be compared. Large series of men undergoing surgery at high-volume centers have been published with long-term follow-up and include both pathologic outcomes and biochemical outcomes (Table 11–1). Smith et al (2007) reported lower rates of positive surgical margins in the robotic group compared with the open group (15% vs 35%, $p < .001$). Similar rates of positive surgical margins have been reported by Ahlering et al (2004) (16.7%), Menon et al (2007) (11%), and Patel et al (2010) (10.6%) and are likely not significantly different when compared with radical retropubic prostatectomy. In two large robotic series, the risk of positive margin was 4% and 13% in pT2 and 34% and 35% in pT3, respectively (Badani et al, 2007; Patel et al, 2008). The risk of biochemical recurrence after robotic prostatectomy appears to be low and comparable with that of open prostatectomy. At median follow-up of 22 months, Badani et al (2007) reported 5-year actuarial biochemical-free survival of 84%. Longer follow-up is required to evaluate if there are significant differences in recurrence-free, and more importantly, cancer-specific survival. Using the SEER-Medicare Linked Database, Hu et al (2009) did not find a difference in rates of utilization of secondary cancer treatments, such as androgen deprivation and radiation therapy, for men undergoing minimally invasive versus open surgery, suggesting that cancer outcomes were similar. Only a single prospective, randomized trial has compared the open and robotic techniques (Yaxley et al, 2016) and found no significant difference in *early* outcomes (12 weeks) with respect to urinary, sexual functional, and oncologic outcomes.

After open prostatectomy, continence rates 1 year after surgery are expected to be ≥90%. Most single-institution series of robotic prostatectomy report comparable results, with ≥93% of men remaining continent 12 months after surgery (Table 11–2). Although there do not appear to be significant differences, men undergoing robotic prostatectomy may have more rapid return of continence. However, data from Hu et al (2009) suggest that men undergoing minimally invasive prostatectomy may have worse urinary outcomes compared with open prostatectomy. The population-based study found an increase in diagnosis of both incontinence and erectile dysfunction. It is important to note that the study did not differentiate between laparoscopic and robotic surgery, covered the early period of minimally invasive prostatectomy (2003–2007), and relied on Medicare claims rather than validated surveys to assess outcomes.

Table 11–1. Perioperative and oncologic outcomes of robot-assisted laparoscopic radical prostatectomy from select published series.

Series	No.	OR time (mean)	EBL (mean)	Hospital stay (d)	Positive margins pT2 (%)	Positive margins pT3 (%)	Positive margins Overall (%)	Biochemical recurrence (%)
Ahlering et al (2004)	60	231	103	—	9	—	16.7	—
Joseph et al (2006)	325	180	196	—	11	—	13	—
Smith et al (2007)	100	208[a]	141[a]	1.1	9	50	15	16[b,c]
Badani et al (2007)	2766	154	142	1.14	13	35	12	7.3
Zorn et al (2007a)	744	234	222	1.4	13	45	19	6.9
Patel et al (2008)	1500	105	111	1	4	33	9	5
Murphy et al (2009)	400	186	[d]	3.1	10	42	19	13
Sukumar et al (2014)	4803	—	—	—	11.2	50.5[e]	25	9.8

[a] Chan RC et al: Effect of a large prostate gland on open and robotically assisted laparoscopic radical prostatectomy. BJU Int 2008;101:1140.

[b] Barocas DA et al: Robotic assisted laparoscopic prostatectomy versus radical retropubic prostatectomy for clinically localized prostate cancer: Comparison of short-term biochemical recurrence-free survival. J Urol 2010;183:990.

[c] Actuarial survival.

[d] Transfusion rate 2.5%.

[e] pT3–T4 disease.

Table 11–2. Urinary outcomes after robot-assisted laparoscopic radical prostatectomy from select series.

Series	No.	Urinary continence rate (months)				Anastomotic stricture rate (%)
		3	6	12	>12	
Joseph et al (2006)	325	93	96	—	—	2.1
Patel (2007)	500	89	95	97	—	—
Zorn et al (2007b)	300	47	68	90	92	1.4
Menon et al (2007)	1142	—	—	84	—	—
Murphy et al (2009)	395	—	—	91	95	3.8
Patel et al (2010)	1100	85	96	97	98	—

The enhanced three-dimensional and magnified visualization of the da Vinci system has led to a better appreciation and renewed consideration of the neuroanatomy of the prostate and parasympathetic innervation responsible for male erections. Techniques developed during the evolution of robotic prostatectomy to improve preservation of nerve bundles include high anterior release of the periprostatic fascia (coined the "Veil of Aphrodite") and minimizing the use of thermal energy during dissection around the neurovascular bundles. Whether these maneuvers ultimately improve erectile function is unclear, but the reexamination of technique and anatomy has led to alterations in both minimally invasive and open surgical operations; it is difficult to determine which approach yields the best sexual function. Overall rates of potency after open prostatectomy have been reported to approach 70% but are largely dependent on baseline function and age (Table 11–3). Approximately 60–70% of patients undergoing bilateral nerve-sparing robotic prostatectomy can be expected to have erections 12 months after surgery. As mentioned, Hu et al (2009) reported an increased diagnosis of erectile dysfunction (26.8 vs 19.2 per 100 person-years) in men undergoing minimally invasive prostatectomy. They also noted that the minimally invasive approach was associated with shorter hospitalization, lower rates of blood transfusion, fewer respiratory and surgical complications, and fewer anastomotic strictures. However, they noted an increased rate of genitourinary complications. Table 11–4 summarizes complications in published robotic prostatectomy series.

▶ Radical Cystectomy

Similarly to laparoscopic radical prostatectomy, laparoscopic cystectomy was reported to be feasible early in the evolution of laparoscopy (1992) but was infrequently performed because of the technical challenges and limitations in instrumentation, prolonged operative time, and need for complex reconstruction. With increasing laparoscopic skills and experience with radical prostatectomy, more reports of laparoscopic cystectomy emerged, and the operation developed over the past decade, with robot-assisted cystectomy a natural progression given the benefits provided by the robot. Nevertheless, it remains a difficult operation, given the need

Table 11–3. Sexual function outcomes after robot-assisted laparoscopic radical prostatectomy from select series.

Series	No.	Mean age (years)	Follow-up (months)	Nerve-sparing (%)		Intercourse (%)		Overall potency % (months)			
				U	B	U	B	3	6	12	>18
Joseph et al (2006)	325	60	12	24	70	58	81	—	—	81	—
Patel (2007)	200	63	12	—	—	—	—	—	70	78	—
Zorn et al (2007b)	258	59	24	26	60	62	83	53	61	80	84
Menon et al (2007)	1142	60	12	25	33	74	97	—	—	70	100
Tewari et al (2008)	215	60	12	11	85	—	87	—	—	87	—
Murphy et al (2009)	248	60	12	28	65	—	—	—	—	62	—
Patel et al (2010)	404	58	12	0	100	—	97	69	82	92	97

U = unilateral; B = bilateral.

Table 11–4. Reported complications after robot-assisted laparoscopic radical prostatectomy from select series.

Series	No.	Overall	Clavien ≥III	Death	Bowel injury	Blood transfusion	Neuropraxia	Urine leak	Thromboembolic event	Urinary retention
Joseph et al (2006)	325	10	—	0	0.3	1.3	0.6	1.2	1.5	—
Patel (2007)	1500	4.4	—	0	0.13	0.5	—	1.4	0.33	0.3
Zorn et al (2007b)	300	10.6	—	—	0	1.7	1.4	1.4	0.6	—
Badani et al (2007)	2766	12.2	0.6	<0.01	—	1.5	—	—	—	—
Murphy et al (2009)	400	15.8	5.3	0	1.2	2.5	—	4.5	—	—
Novara et al (2010)	415	21.6	3.2	—	1.2	5.3	0.9	6.7	0.2	1.4
Lasser et al (2010)	239	17	5.4	0.4	0.4	4.2	1.3	2.9	0.4	0.8
Coelho et al (2010)	2500	5.1	0.96	0	0.08	0.48	0	1.4	0.32	0.52

for meticulous cancer excision, extended lymphadenectomy in all cases, and urinary tract reconstruction.

The primary indication for robotic cystectomy includes patients with muscle-invasive or high-risk/refractory non-invasive urothelial carcinoma of the bladder. The operation has been reported to be feasible in both men (cystoprostatectomy) and women (anterior pelvic exenteration), and it also includes removal of the pelvic lymph nodes. Most surgeons perform the extirpative portion of the operation using the robot, and then make a small lower abdominal incision to extract the specimens as well as perform the urinary diversion; however, a purely minimally invasive approach to the entire operation has been described and is feasible, but it is time consuming and potentially of little additional benefit.

Most series regarding robotic cystectomy are single-institution, nonrandomized case series. Nix et al (2010) report the first prospective, randomized trial comparing robotic versus open radical cystectomy for bladder cancer in a total of 41 men. The primary endpoint evaluated was the lymph node yield, and the mean numbers removed in the robotic and open groups were 19 and 18, respectively. There were no significant differences with respect to positive surgical margins or perioperative outcomes, including length of hospitalization and overall complication rate. The same group reported no case of positive surgical margin in 100 consecutive cases of robotic radical cystectomy (Pruthi et al, 2010), while the International Robotic Cystectomy Consortium (Hellenthal et al, 2010) reported a rate of 6.8% in 513 patients—1.5% for stage ≤pT2, 8.8% for pT3, and 39% for pT4. Further evaluation, beyond surrogates such as lymph node number and margin status, is necessary to assess the oncologic efficacy of the operation.

Yuh et al (2009) prospectively analyzed the impact of robotic cystectomy on quality of life in 34 patients undergoing surgery. Despite a significant number (38%) requiring chemotherapy, quality of life as assessed by the Functional Assessment of Cancer Therapy-Bladder instrument showed improvements at 3 months after surgery and total scores at 6 months exceeding preoperative scores.

Kauffman et al (2010) characterized the complications in 79 consecutive patients undergoing robotic radical cystectomy. Within 90 days of surgery, 49% experienced a complication of which 79% were low grade, including infectious (41%) or gastrointestinal (27%). Of those patients, 16% had a high-grade complication and were significantly associated with age older than 65 years, operative blood loss ≥500 mL, and intravenous fluids >5 L. These compare favorably with open radical cystectomy. Other studies suggest that advantages of the robotic approach include reduced blood loss, lower transfusion rate, shorter hospital stay, and earlier resumption of regular diet (Wang et al, 2008).

A recent meta-analysis of the four randomized controlled trials included a total of 239 cases (Tan et al, 2018). The two techniques appear similar with no significant differences when examining lymph node yield, positive surgical margins, and perioperative complications and mortality. However, the robotic approach was associated with reduced blood loss while the open operation had shorter operative time.

UPPER URINARY TRACT OPERATIONS

Pyeloplasty

The management of ureteropelvic junction (UPJ) obstruction has evolved, and various approaches have been attempted, including traditional open surgery, endoscopic, and laparoscopic/robotic. The open operation options include dismembered, flap, and incisional-intubated types, based on the specific ureteral anatomy, size of the renal pelvis, and the presence or absence of a crossing renal vessel. All of these have been applied using either pure laparoscopy or robotic assistance, and the outcomes must be compared against the gold standard of open techniques, with contemporary series reporting success in >90% of cases.

The first laparoscopic adult pyeloplasty was reported in 1993, where a dismembered pyeloplasty was performed similarly to the open technique. Since that time, larger series of laparoscopic pyeloplasty have been reported with resolution of UPJ obstruction in >90%. Many would consider it the gold standard in the management of cases of adult UPJ obstruction today. Nevertheless, it remained performed largely by experienced surgeons at academic referral centers given the low incidence of condition and technical challenges of the complex reconstruction, including cutting of the pelvis and ureter and subsequent suturing. Robotic assistance was first reported for pyeloplasty in 2002, given the potential to facilitate tailoring the pelvis and ureter, and suturing the anastomosis. Outcomes have been excellent, with short-term resolution of the UPJ obstruction to be >95%; many of these series have included cases of secondary UPJ obstruction after failed prior therapy (eg, endopyelotomy) (Singh et al, 2010). Hemal et al (2010) compared robotic and laparoscopic pyeloplasty in 60 patients. Advantages of the robotic method included shorter operative time, less blood loss, and shorter hospitalization (2 vs 3.5 days), with similar success rates (97% robotic vs 100% laparoscopic).

Mufarrij et al (2008) reported the combined robotic pyeloplasty experience in 140 patients from three medical centers. The mean operative time was 217 minutes, with length of stay 2.1 days. Resolution of UPJ obstruction on the first follow-up imaging study was 96% and the complication rate was 10%, and the mean follow-up was 29 months. Gupta et al (2010) reported similar outcomes in 85 patients, with 97% success at 14 months' follow-up.

Partial Nephrectomy

The management of renal tumors has evolved rapidly over the past 20 years, with the advent of laparoscopic techniques as well as the application of ablative technologies. The first laparoscopic radical nephrectomy, performed in 1990, represented a shift toward minimally invasive renal surgery, and subsequent data have proven that equivalent cancer control is achieved by the laparoscopic technique. The excellent oncologic outcomes combined with the ease of completely removing the kidney, even for small masses, have contributed to the relative underutilization of nephron-sparing surgery (Dulabon et al, 2010). Other publications have suggested that greater efforts should be made to spare as much normal renal parenchyma as possible, and that partial nephrectomy needs to be performed more often (McKiernan et al, 2002; Huang et al, 2006). However, open partial nephrectomy has been viewed as a difficult operation because of patient morbidity, expectation of significant bleeding, and concerns surrounding surgical margins. All these factors are relevant in the discussion of laparoscopic partial nephrectomy. Although the first laparoscopic partial nephrectomy was reported in 1993, acceptance and dissemination were relatively slow, given the technical skills required to ensure complete tumor excision and to achieve hemostasis.

Large series from highly experienced laparoscopic surgeons confirm both the oncologic adequacy of laparoscopic partial nephrectomy and the safety and low risk of complications. Improved instrumentation, such as vascular and bulldog clamps, and application of energy sources facilitated tumor excision and renorrhaphy. However, concerns still surrounded renal injury, given the ischemic time required for the procedure, most often performed without renal hypothermia. Thus, hand assistance was proposed as an aid to reduce warm ischemia time. Likewise, the robot may also facilitate minimally invasive partial nephrectomy by making specific aspects easier and thereby shorten the duration of vascular occlusion. Minimally invasive partial nephrectomy, either laparoscopic or robotic, is a challenging operation requiring meticulous tumor excision, control of bleeding, and closure of the collecting system with the simultaneous need for alacrity and underlying risk of significant bleeding.

Gettman et al (2004) reported the initial series of partial nephrectomy procedures using the da Vinci robot. They demonstrated that the operation was feasible, with no case of conversion to open, and operative time averaged 215 minutes. In 8 of the 13 cases, renal cooling was achieved by an intra-arterial catheter, while the remainder underwent partial nephrectomy with vascular clamping alone (warm ischemia). Another report compared outcomes between robotic partial nephrectomy performed by an experienced open partial nephrectomy surgeon and laparoscopic partial nephrectomy performed by experienced laparoscopic experts (Deane et al, 2008). There were no significant differences in operative time, operative blood loss, and warm ischemia time, suggesting that robotic assistance enabled those less experienced with laparoscopy to achieve good outcomes. A larger, contemporary single-surgeon study found no difference in the techniques with respect to blood loss and positive surgical margins; however, the robotic approach had advantages of shorter operative and warm ischemia time as well as length of hospitalization (Wang et al, 2009).

Since 2013, with robotic partial nephrectomy, it has been feasible to achieve outcomes similar to those obtained with laparoscopic partial nephrectomy (Scoll et al, 2010; Benway et al, 2009). Rates of positive surgical margin are <5%, and complications typically occur in <10% of patients. Potential complications include wound infection, urinary leak/urinoma, and ileus. Major complications include bleeding and need for open surgical conversion.

Newer techniques have been developed and tested to obtain hemostasis, including the use of hemostatic agents, thermal energy devices, and novel sutures and suturing aids. In addition, selective clamping of renal artery branches or omission/early release of vascular occlusion has been performed to reduce the potential for renal injury. These modifications have allowed surgeons to approach more difficult tumors—those >4 cm, endophytic location, multiple masses, and those located adjacent to the renal helium and large vessels. Long-term data are required to confirm cancer control equivalent to radical nephrectomy and/or open partial nephrectomy and preservation of renal function. Most agree, however, that the availability of the robot permits surgeons with less experience with laparoscopy to perform the procedure and shortens the learning curve for the operation and has led to widespread adoption and acceptance (Foerster et al, 2018).

PEDIATRIC OPERATIONS

In urology, robotic assistance has been applied to nearly every pediatric operation that has been accomplished via laparoscopy. The advantages may be greater in this domain, given the preponderance of reconstructive, rather than extirpative, procedures. Conversely, the pediatric population poses unique challenges—limited working space within the body, need for smaller ports and instruments, restricted access to the smaller patient by the large surgical cart, and limited haptics on delicate tissue. In addition, the relative benefits of minimally invasive surgery on postoperative recovery and morbidity may be less significant than in the adult. Although a survey of parental satisfaction of open and robotic pyeloplasty using a validated surgery demonstrated greater satisfaction with the robotic approach, the differences were not at great as anticipated (Freilich et al, 2010).

The most common robotic operation in children is pyeloplasty, and the early cumulative experience demonstrates that the outcomes are not significantly different from open pyeloplasty (Lee et al, 2006; Olsen et al, 2007; Song et al, 2017). Success is expected in >95% of cases with complication rates <20%. Other applications of the robot include heminephrectomy for nonfunctioning polar moiety in a duplicated system, extravesical ureteral reimplantation, and bladder augmentation. The role of robotics in operations such as adrenalectomy and total nephrectomy are unclear, given the ease in performing the procedure via traditional laparoscopy and inability to take advantage of the added dexterity and precision provided by the robot.

SINGLE-SITE ROBOTIC SURGERY

The newest variation of minimally invasive urologic surgery is the use of only one incision through which all the instruments and laparoscope are introduced, and the procedure is performed, best termed **laparoendoscopic single-site surgery (LESS)**. Tools have been developed to facilitate the ease of surgery and ergonomics, including smaller deflectable-tip laparoscopes, bent and articulating laparoscopic instruments, and single-port access systems. A major challenge of LESS is the need to adapt to new laparoscopic instruments and the "sword fighting" and crossing of instruments both inside and outside of the body. The da Vinci robot has been successfully applied to LESS in performing prostatectomy, radical and partial nephrectomy, and dismembered pyeloplasty (Kaouk et al, 2008). It is expected that further refinements of the robotic system will permit better adaptation to LESS, and these are currently available as modifications to the da Vinci Si system with FDA approval in 2014 and the recent clinical availability of a new da Vinci SP single-port robotic system.

COST-EFFECTIVENESS

A major criticism of the robotic system is the associated financial costs. Each da Vinci surgical system is approximately $1.5 million with annual maintenance requirements of over $100,000. In addition, the costs of disposables associated with the robot exceed those of traditional laparoscopy. Bolenz et al (2010) compared the costs associated with robotic, laparoscopic, and open prostatectomy for prostate cancer in 643 patients treated over a 6-year period. Robotic prostatectomy was associated with the highest cost, due to differences in surgical supply and operating room cost. Even with improvements in operative time, rapid time to discharge, and increase in surgical volume, robotic prostatectomy is likely to remain more expensive than other techniques (Lotan, 2010). Given the unproven improvement in outcomes with robotic assistance, physicians should be cautious in the wholesale application to all minimally invasive operations and attempts should be made to systematically study newer surgical technologies. In the future, these economic factors will only be more relevant for both surgeons and patients, given the explosion of healthcare expenditure, greater scrutiny of outcome and quality of care, and inevitable cost-cutting measures in the era of healthcare reform.

TRAINING IN ROBOTICS

The introduction and proliferation of new technology and surgical techniques has raised questions regarding how best to train both residents and practicing urologists. Currently, there are no established systems to ensure surgeon competency and safety with robotic urological surgery. These issues have been raised by a panel of experts (Zorn et al, 2009), and future guidelines should be expected to help standardize the process of robotic education, training, proctoring, and credentialing.

BIBLIOGRAPHY

Radical Prostatectomy (see "Lower Urinary Tract Operations" section)

Ahlering TE et al: Robot-assisted versus open radical prostatectomy: A comparison of one surgeon's outcomes. Urology 2004;63:819. [PMID: 15134953]

Badani KK et al: Evolution of robotic radical prostatectomy: Assessment after 2766 procedures. Cancer 2007;110:1951. [PMID: 17893904]

Barocas DA et al: Robotic assisted laparoscopic prostatectomy versus radical retropubic prostatectomy for clinically localized prostate cancer: Comparison of short-term biochemical recurrence-free survival. J Urol 2010;183:990. [PMID: 20083261]

Chan RC et al: Effect of a large prostate gland on open and robotically assisted laparoscopic radical prostatectomy. BJU Int 2008;101:1140. [PMID: 18399829]

Coelho RF et al: Early complication rates in a single-surgeon series of 2500 robotic-assisted radical prostatectomies: Report applying a standardized grading system. Eur Urol 2010;57(6):945–952. [PMID: 20181424]

Hu JC et al: Comparative effectiveness of minimally invasive vs. open radical prostatectomy. JAMA 2009;302:1557. [PMID: 19826025]

Joseph JV et al: Robotic extraperitoneal radical prostatectomy: An alternative approach. J Urol 2006;175:945. [PMID: 16469589]

Lasser MS et al: An unbiased prospective report on perioperative complications of robot-assisted laparoscopic radical prostatectomy. Urology 2010;75:1083. [PMID: 20110114]

Menon M et al: Vattikuti Institute prostatectomy: Contemporary technique and analysis of results. Eur Urol 2007;51:648. [PMID: 17097214]

Murphy DG et al: Operative details and oncological and functional outcome of robotic-assisted laparoscopic radical prostatectomy: 400 cases with a minimum of 12 months follow-up. Eur Urol 2009;55:1358. [PMID: 19147274]

Novara G et al: Prospective evaluation with standardized criteria for postoperative complications after robotic-assisted laparoscopic radical prostatectomy. Eur Urol 2010;57:363. [PMID: 19944519]

Patel VR et al: Robotic radical prostatectomy: Outcomes of 500 cases. BJU Int 2007;99:1109. [PMID:17437441]

Patel VR et al: Robot-assisted laparoscopic radical prostatectomy: Perioperative outcomes of 1500 cases. J Endourol 2008;22:2299. [PMID: 18837657]

Patel VR et al: Continence, potency and oncological outcomes after robotic-assisted radical prostatectomy: Early trifecta results of a high-volume surgeon. BJU Int 2010;106(5):696–702. [PMID: 20707793]

Smith JA Jr et al: A comparison of the incidence and location of positive surgical margins in robotic-assisted laparoscopic radical prostatectomy and open retropubic radical prostatectomy. J Urol 2007;178:2385. [PMID: 17936849]

Tewari A et al: Cancer control and the preservation of neurovascular tissue: How to meet the competing goals during robotic radical prostatectomy. BJU Int 2008;101:1013. [PMID: 18261153]

Yaxley JW et al: Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet 2016;388:1057. [PMID: 27474375]

Zorn KC et al: da Vinci robot error and failure rates: Single institution experience on a single three-arm robot unit of more than 700 consecutive robot-assisted laparoscopic radical prostatecomies. J Endourol 2007a;21:1341. [PMID: 18042027]

Zorn KC et al: Robotic-assisted laparoscopic prostatectomy: Functional and pathologic outcomes with interfascial nerve preservation. Eur Urol 2007b;61:755. [PMID: 17084520]

Radical Cystectomy (see "Lower Urinary Tract Operations" section)

Hellenthal NJ et al: Surgical margin status after robot assisted radical cystectomy: Results from the International Robotic Cystectomy Consortium. J Urol 2010;184:87. [PMID: 20478596]

Kauffman EC et al: Critical analysis of complications after robotic-assisted radical cystectomy with identification of preoperative and operative risk factors. BJU Int 2010;105:520. [PMID: 19735257]

Nix J et al: Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: Perioperative and pathologic results. Eur Urol 2010;57:196. [PMID: 19853987]

Parra RO et al: Laparoscopic cystectomy: Initial report on a new treatment for the retained bladder. J Urol 1992;148:1140. [PMID: 1404624]

Pruthi RS et al: Robotic radical cystectomy for bladder cancer: Surgical and pathological outcomes in 100 consecutive cases. J Urol 2010;183:510. [PMID: 20006884]

Sukumar S et al: Oncological outcomes after robot-assisted radical prostatectomy: long-term follow-up in 4803 patients. BJU Int. 2014 Dec;114(6):824–31. doi: 10.1111/bju.12404.

Tan J et al: Robotic-assisted versus open radical cystectomy in bladder cancer: A meta-analysis of four randomized controlled trials. Int J Med Robot 2018;14. [PMID: 29027351]

Wang GJ et al: Robotic vs. open radical cystectomy: Prospective comparison of perioperative outcomes and pathological measures of early oncological efficacy. BJU Int 2008;101:89. [PMID: 17888044]

Yuh B et al: Short-term quality-of-life assessed after robot-assisted radical cystectomy: A prospective analysis. BJU Int 2009;103:800. [PMID: 19021613]

Pyeloplasty (see "Upper Urinary Tract Operations" section)

Gupta NP et al: Outcome analysis of robotic pyeloplasty: A large single-centre experience. BJU Int 2010;105:980. [PMID: 19874304]

Hemal AK et al: Laparoscopic pyeloplasty versus robotic pyeloplasty for ureteropelvic junction obstruction: A series of 60 cases performed by a single surgeon. Can J Urol 2010;17:5012. [PMID: 20156381]

Mufarrij PW et al: Robotic dismembered pyeloplasty: A 6-year, multi-institutional experience. J Urol 2008;180:1391. [PMID: 18707739]

Singh I et al: Robot-assisted pyeloplasty: Review of the current literature, technique and outcome. Can J Urol 2010;17:5099. [PMID: 20398449]

Partial Nephrectomy (see "Upper Urinary Tract Operations" section)

Benway BM et al: Robot assisted partial nephrectomy versus laparoscopic partial nephrectomy for renal tumors: A multi-institutional analysis of perioperative outcomes. J Urol 2009;182:866. [PMID: 19616229]

Deane LA et al: Robotic versus standard laparoscopic partial/wedge nephrectomy: A comparison of intraoperative and perioperative results from a single institution. J Endourol 2008;22:947. [PMID: 18397157]

Dulabon LM et al: Trends in renal tumor surgery delivery within the United States. Cancer 2010;116:2316. [PMID: 20225227]

Foerster B et al: Robot-assisted partial nephrectomy: systematic review of functional results. Curr Opin Urol 2018;28:123. [PMID: 29278584]

Gettman MT et al: Robotic-assisted laparoscopic partial nephrectomy: Technique and initial clinical experience with DaVinci robotic system. Urology 2004;64:914. [PMID: 15533477]

Huang WC et al: Chronic kidney disease after nephrectomy in patients with renal cortical tumours: A retrospective cohort study. Lancet Oncol 2006;7:735. [PMID: 16945768]

McKiernan J et al: Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology 2002;59:816. [PMID: 12031359]

Scoll BJ et al: Robot-assisted partial nephrectomy: A large single-institutional experience. Urology 2010;75:1328. [PMID: 20080290]

Wang AJ et al: Robotic partial nephrectomy versus laparoscopic partial nephrectomy for renal cell carcinoma: Single-surgeon analysis of >100 consecutive procedures. Urology 2009;73:306. [PMID: 19038419]

Pediatric Operations

Freilich DA et al: Parental satisfaction after open versus robot assisted laparoscopic pyeloplasty: Results from modified Glasgow Children's Benefit Inventory Survey. J Urol 2010;183:704. [PMID: 20022046]

Lee RS et al: Pediatric robot assisted laparoscopic dismembered pyeloplasty: Comparison with a cohort of open surgery. J Urol 2006;175:683. [PMID: 16407025]

Olsen LH et al: Pediatric robot assisted retroperitoneoscopic pyeloplasty: A 5-year experience. J Urol 2007;178;2137. [PMID: 17870122]

Song SH et al: A comparative study of pediatric open pyeloplasty, laparoscopy-assisted extracorporeal pyeloplasty, and robot-assisted laparoscopic pyeloplasty. PLoS One. 2017 Apr 20;12(4):e0175026. doi: 10.1371/journal.pone.0175026. eCollection 2017.

Single-Site Robotic Surgery

Kaouk JH et al: Robotic single-port transumbilical surgery in humans: Initial report. BJU Int 2008;103:366. [PMID: 18778351]

Cost-Effectiveness

Bolenz C et al: Cost comparison of robotic, laparoscopic, and open radical prostatectomy for prostate cancer. Eur Urol 2010;57:453. [PMID: 19931979]

Lotan Y: Economics of robotics in urology. Curr Opin Urol 2010;20:92. [PMID: 19875963]

Training in Robotics

Zorn KC et al: Training, credentialing, proctoring and medicolegal risks of robotic urological surgery: Recommendations of the society of urologic robotic surgeons. J Urol 2009;182:1126. [PMID: 19625032]

Urinary Obstruction & Stasis

12

Marshall L. Stoller, MD; &
Tom F. Lue, MD, FACS, ScD (Hon)

Urinary obstruction and stasis are important urologic disorders because of their potential to damage the kidney. Ureteral obstruction leads to hydroureteronephrosis, and eventually kidney atrophy that may terminate in renal failure. Furthermore, obstruction often is complicated by infection, which can result in systemic complications and cause additional damage to other organs.

CAUSES, TYPES, CHARACTERISTICS, AND SYMPTOMS

Classification

Obstruction may be classified according to cause (congenital or acquired), duration (acute or chronic), degree (partial or complete), and level (upper or lower urinary tract).

Etiology

Congenital anomalies, more common in the urinary tract than in any other organ system, are generally obstructive. In adult life, many types of acquired obstructions can occur.

A. Congenital

The common sites of congenital narrowing are the external meatus in boys (meatal stenosis) or just inside the external urinary meatus in girls, the distal urethra (stenosis), posterior urethral valves, ectopic ureters, ureteroceles, and the ureterovesical and ureteropelvic junctions (Beganović et al, 2007; Tan and Smith, 2004). Another congenital cause of urinary stasis is damage to sacral roots 2–4 as seen in spina bifida and myelomeningocele. Vesicoureteral reflux causes both vesical and renal stasis (see Chapter 13).

B. Acquired

Acquired obstructions are numerous and may be primary in the urinary tract or secondary to retroperitoneal lesions that invade or compress the urinary passages. Among the common causes are (1) urethral stricture secondary to infection or injury; (2) benign prostatic hyperplasia or cancer of the prostate; (3) vesical tumor involving the bladder neck or one or both ureteral orifices; (4) local extension of cancer of the prostate or cervix into the base of the bladder, occluding the ureters; (5) compression of the ureters at the pelvic brim by metastatic nodes from cancer of the prostate or cervix; (6) ureteral stone(s); (7) retroperitoneal fibrosis or malignant tumor; and (8) pregnancy.

Neurogenic dysfunction affects principally the bladder. The upper tracts are damaged secondarily by ureterovesical obstruction or reflux and, often, by complicating infection. Severe constipation, especially in children, can cause bilateral hydroureteronephrosis from compression of the lower ureters.

Elongation and kinking of the ureter secondary to vesicoureteral reflux commonly lead to ureteropelvic obstruction and hydronephrosis. Unless a voiding cystourethrogram is obtained in children with this lesion, the primary cause may be missed and improper treatment undertaken.

Pathogenesis and Pathology

Obstruction and neuropathic vesical dysfunction have the same effects on the urinary tract. These changes can best be understood by considering the effects of (1) a severe meatal stricture on the lower tract (distal to the bladder neck), (2) a large obstructing prostate on the midtract (bladder), and (3) an impacted stone in the ureter on the upper tract (ureter and kidney).

A. Lower Tract (eg, Urethral Stricture)

Hydrostatic pressure proximal to the obstruction causes dilation of the urethra. The wall of the urethra may become thin, and a diverticulum may develop. If the urine becomes infected, urinary extravasation may occur, and periurethral abscess can result. The prostatic ducts may become widely dilated.

B. Midtract (eg, Prostatic Hyperplasia)

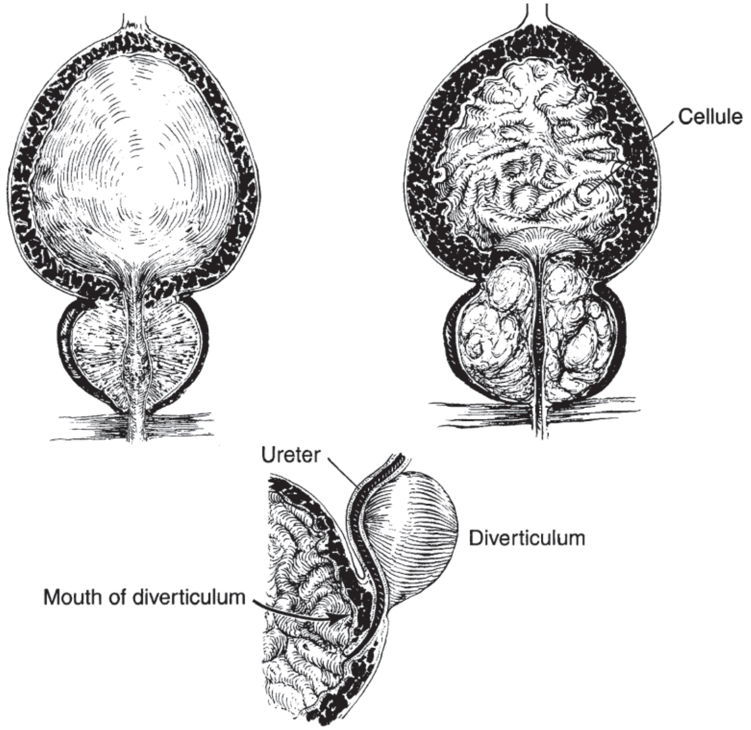
In the earlier stages (compensatory phase), the muscle wall of the bladder becomes hypertrophied and thickened. With decompensation, it becomes less contractile and, therefore, weakened (Lieber et al, 2010).

1. Stage of compensation—To balance the increasing outlet resistance, the bladder musculature hypertrophies. Its thickness may double or triple. Complete emptying of the bladder thus becomes possible.

Hypertrophied muscle may be seen endoscopically. With secondary infection, the effects of infection are often superimposed. There may be edema of the submucosa, which may be infiltrated with plasma cells, lymphocytes, and polymorphonuclear cells. At cystoscopy, surgery, or autopsy, the following evidence of this compensation may be visible (Figure 12–1).

A. Trabeculation of the bladder wall—The wall of the distended bladder is normally smooth. With hypertrophy, muscle bundles with deposits of interstitial collagen fibers become taut and give a coarsely interwoven appearance to the mucosal surface, commonly described as **trabeculations.** The trigonal muscle and the interureteric ridge, which normally are only slightly raised above the surrounding tissues, respond to obstruction by hypertrophy of their smooth musculature. The ridge then becomes prominent. This trigonal hypertrophy causes increased resistance to urine flow in the intravesical ureteral segments. It is this mechanism that causes relative functional obstruction of the ureterovesical junctions, leading to back pressure on the kidney and hydroureteronephrosis. The obstruction increases in the presence of significant residual urine, which further stretches the ureterotrigonal complex (Tanagho and Meyers, 1965). (A urethral catheter relieves the obstruction somewhat by eliminating the trigonal stretch. Definitive prostatectomy leads to permanent release of stretch and gradual softening of trigonal hypertrophy after relief of the obstruction.)

B. Cellules—Normal intravesical pressure is about 30 cm of water at the beginning of micturition. Pressures 2–4 times as great may be reached by the trabeculated (hypertrophied) bladder in its attempt to force urine past the obstruction. This pressure tends to push mucosa between the superficial muscle bundles, causing the formation of small pockets, or cellules (Figure 12–1).



▲ **Figure 12–1.** Changes in the bladder developing from obstruction. ***Upper left:*** Normal bladder and prostate. ***Upper right:*** Obstructing prostate causing trabeculation, cellule formation, and hypertrophy of the interureteric ridge. ***Bottom:*** Marked trabeculation (hypertrophy) of the vesical musculature; diverticulum displacing left ureter.

C. Diverticula—If cellules force their way entirely through the musculature of the bladder wall, they become saccules, then actual diverticula, which may be embedded in perivesical fat or covered by peritoneum, depending on their location. Diverticula have no muscle wall and are therefore unable to expel their contents into the bladder efficiently even after the primary obstruction has been removed. When secondary infection occurs, it is difficult to eradicate; surgical removal of the diverticula may be required. If a diverticulum pushes through the bladder wall on the anterior surface near the ureteral orifice, the ureterovesical junction may become incompetent (see Chapter 14).

D. Mucosa—In the presence of acute infection, the mucosa may be reddened and edematous. This may lead to temporary vesicoureteral reflux in the presence of a "borderline" junction. The chronically inflamed membrane may be thinned and pale. In the absence of infection, the mucosa appears normal.

2. Stage of decompensation—The compensatory power of the bladder musculature varies greatly. One patient with prostatic enlargement may have only mild symptoms of prostatism; however, a large obstructing prostate gland that can be palpated rectally and observed cystoscopically; another may suffer acute retention and yet have a gland of normal size on rectal palpation and what appears to be only a mild obstruction cystoscopically.

In the face of progressive outlet obstruction, possibly aggravated by prostatic infection with edema or by congestion, decompensation of the detrusor may occur, resulting in the presence of a large amount of residual urine after voiding. The amount may range up to 500 mL or more.

C. Upper Tract

1. Ureter—In the early stages of obstruction, intravesical pressure is normal while the bladder fills and is increased only during voiding. The pressure is not transmitted to the ureters and renal pelves because of the competence of the ureterovesical "valves." (A true valve is not present; the ureterotrigonal unit, by virtue of its intrinsic structure, resists the retrograde flow of urine.) However, owing to trigonal hypertrophy (see section titled "Trabeculation of the bladder wall") and to the resultant increase in resistance to urine flow across the terminal ureter, there is progressive back pressure on the ureter and kidney, resulting in ureteral dilatation and hydronephrosis. Later, with the phase of decompensation accompanied by residual urine, there is an added stretch effect on the already hypertrophied trigone that increases the resistance to flow at the lower end of the ureter appreciably and induces further hydroureteronephrosis. With decompensation of the ureterotrigonal complex, the valvelike action may be lost, vesicoureteral reflux occurs, and the increased intravesical pressure is transmitted directly to the renal pelvis, aggravating the degree of hydroureteronephrosis (Riccabona, 2010; Routh et al, 2010).

Secondary to the backpressure resulting from reflux or from obstruction by the hypertrophied and stretched trigone or by a ureteral stone, the ureteral musculature thickens in its attempt to propel the urine downward by increased peristaltic activity (stage of compensation). This causes elongation and some tortuosity of the ureter (Figure 12–2). At times, this change becomes marked, and bands of fibrous tissue develop. On contraction, the bands further angulate the ureter, causing secondary ureteral obstruction. Under these circumstances, removal of the obstruction below may not prevent the kidney from undergoing progressive obstruction due to the secondary ureteral obstruction.

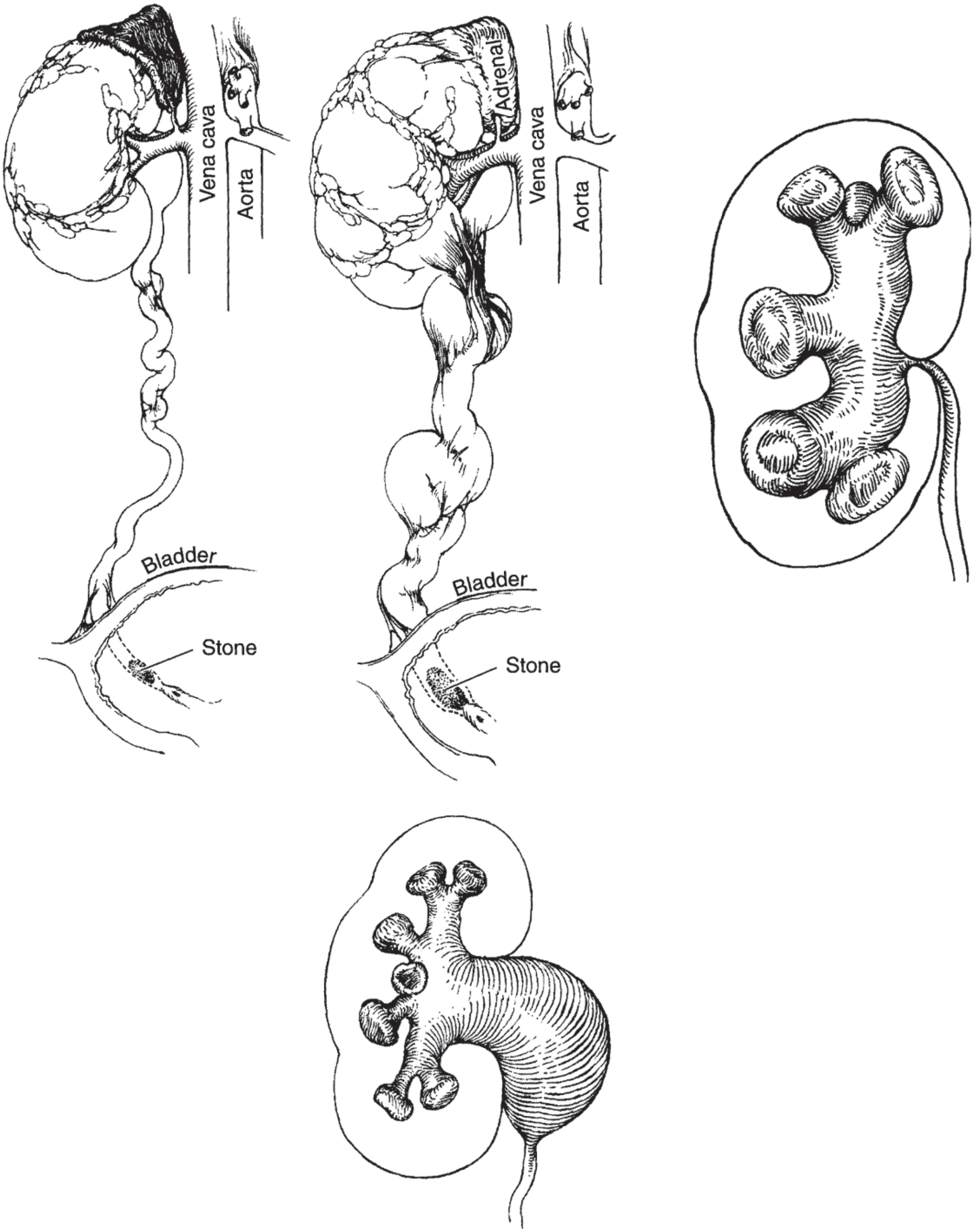
Finally, because of increasing pressure, the ureteral wall becomes attenuated and therefore loses its contractile power (stage of decompensation). Dilatation may be so extreme that the ureter resembles a loop of bowel (Gimpel et al, 2010) (Figure 12–3).

2. Kidney—The pressure within the renal pelvis is normally close to zero. When this pressure increases because of obstruction or reflux, the pelvis and calyces dilate. The degree of hydronephrosis that develops depends on the duration, degree, and site of the obstruction (Figure 12–4). The higher the obstruction, the greater the effect on the kidney. If the renal pelvis is entirely intrarenal and the obstruction is at the ureteropelvic junction, all the pressure will be exerted on the renal parenchyma (Klein et al, 2010). If the renal pelvis is extrarenal, only part of the pressure produced by a ureteropelvic stenosis is exerted on the parenchyma; this is because the extrarenal pelvis is surrounded by fat and dilates more readily compared to the renal parenchyma, thus "decompressing" the calyces (Figure 12–2).

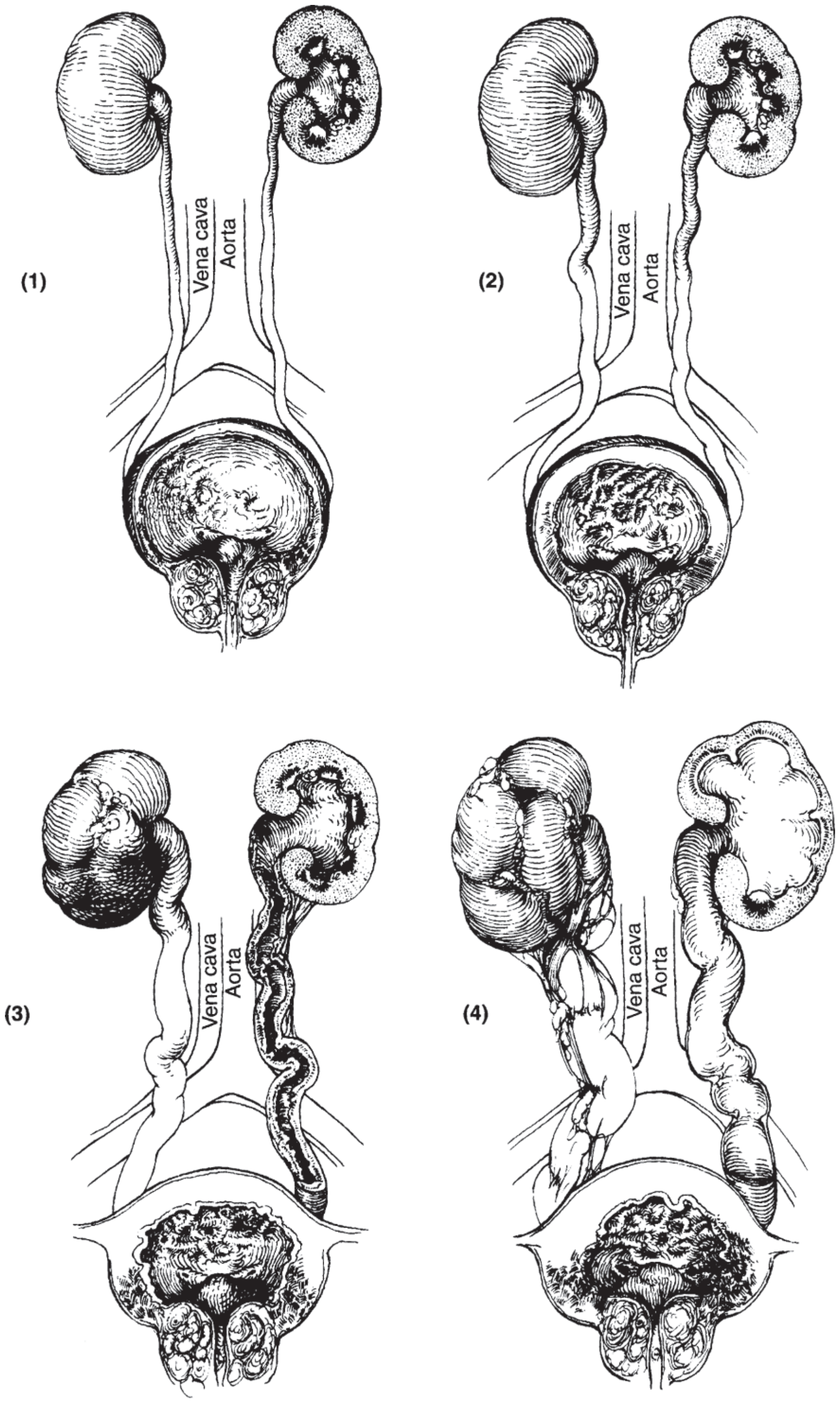
In the earlier stages, the renal pelvic musculature undergoes compensatory hypertrophy in its effort to propel urine past the obstruction. Later, however, the muscle becomes stretched and atonic (and decompensated).

The progression of hydronephrotic atrophy is as follows (Chevalier et al, 2010; Rodriguez, 2004):

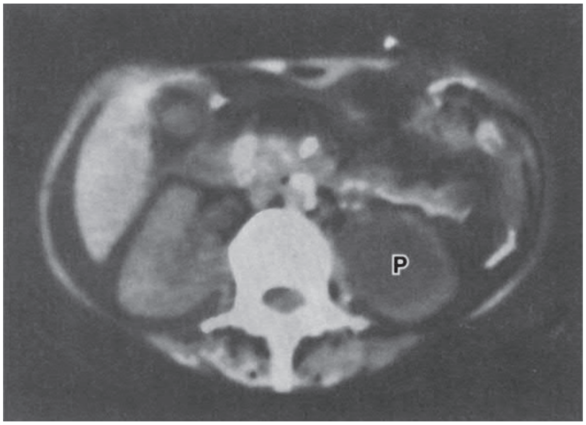
1. The earliest changes in the development of hydronephrosis are seen in the calyces. The end of a normal calyx is concave because of the papilla that projects into it; with increase in intrapelvic pressure, the fornices become blunt and rounded. With persistence of increased intrapelvic pressure, the papilla becomes flattened, then convex (clubbed) as a result of compression enhanced by ischemic atrophy (Figure 12–5). The parenchyma between the calyces is affected to a lesser extent. The changes in the renal parenchyma are due to (a) compression atrophy from increase in intrapelvic pressure (more accentuated with intrarenal pelves) and (b) ischemic atrophy from hemodynamic changes, manifest mainly in arcuate vessels that run at the base of the pyramids parallel to the kidney outline and are more vulnerable to compression between the renal capsule and the centrally increasing intrapelvic pressure.



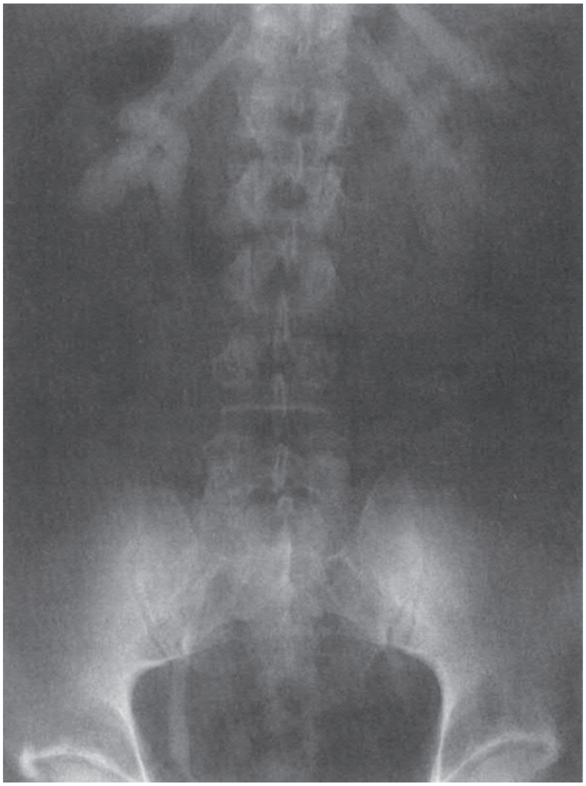
▲ **Figure 12–2.** Mechanisms and results of obstruction. ***Upper left:*** Early stage. Elongation and dilatation of ureter due to mild obstruction. ***Upper center:*** Later stage. Further dilatation and elongation with kinking of the ureter; fibrous bands cause further kinking. ***Upper right:*** Intrarenal pelvis. Obstruction transmits all back pressure to parenchyma. ***Lower:*** Extrarenal pelvis, when obstructed, allows some of the increased pressure to be dissipated by the pelvis.



▲ **Figure 12–3.** Pathogenesis of bilateral hydronephrosis. Progressive changes in bladder, ureters, and kidneys from obstruction of an enlarged prostate: thickening of bladder wall, dilatation and elongation of ureters, and hydronephrosis.



▲ **Figure 12–4.** Hydronephrotic left renal pelvis. Low-density mass (P) in left renal sinus had attenuation value near that of water, suggesting the correct diagnosis. Unless intravenous contrast material is used, differentiation from peripelvic cyst may be difficult.

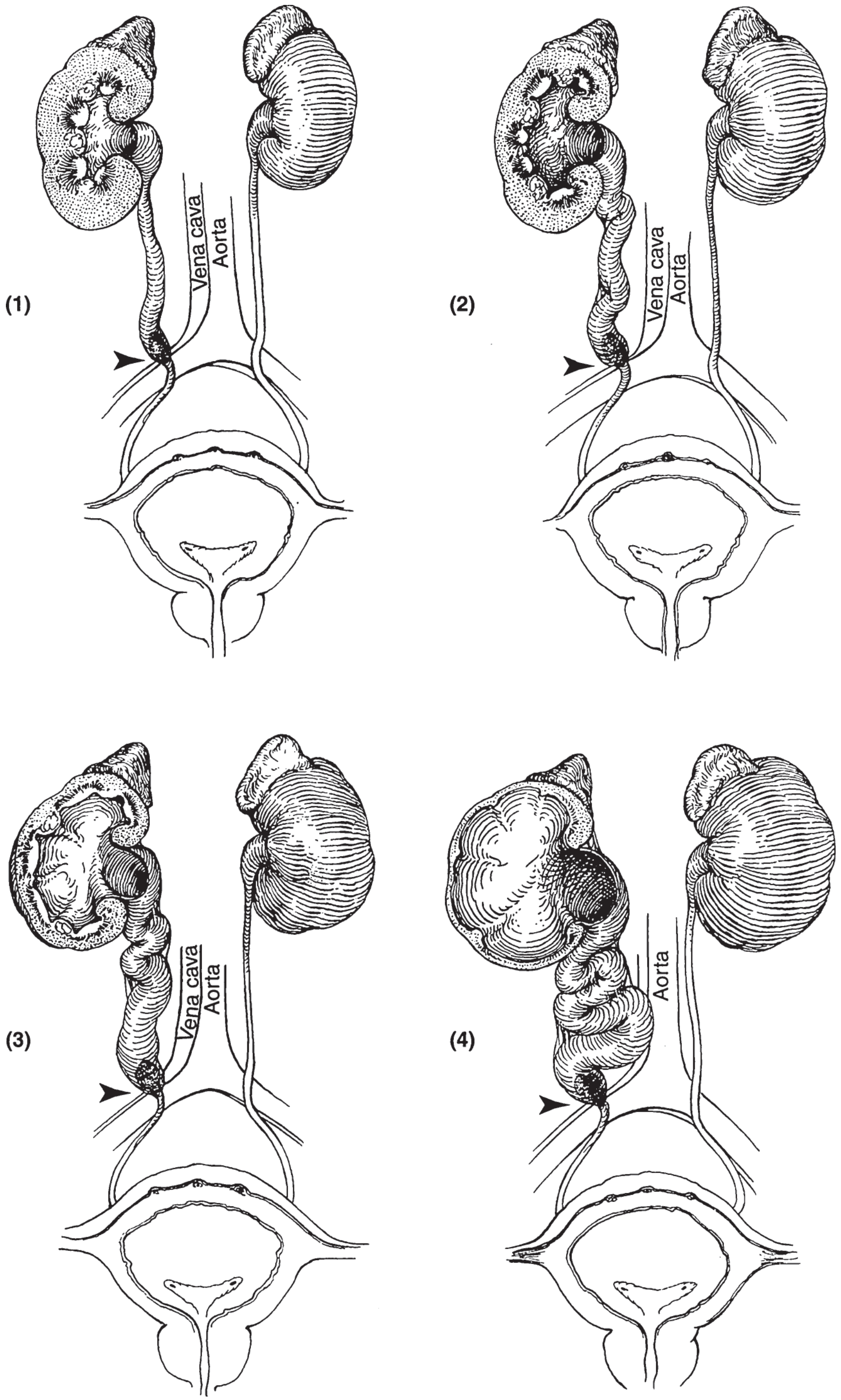


▲ **Figure 12–5.** Lower right ureteral obstruction. Mild to moderate dilatation of the collecting system with rounded blunting of the calyces.

2. This spotty atrophy is caused by the nature of the blood supply of the kidney. The arterioles are "end arteries"; therefore, ischemia is most marked in the areas farthest from the interlobular arteries. As the back pressure increases, hydronephrosis progresses, with the cells nearest the main arteries exhibiting the greatest resistance.
3. This increased pressure is transmitted up the tubules. The tubules become dilated, and their cells atrophy as a result of ischemia. It should be pointed out that a few instances of dilated renal pelves and calyces are not due to the presence of obstruction. Rarely, the renal cavities are congenitally capacious and thus simulate hydronephrosis. More commonly, hydronephrosis may occur in childhood owing to the back pressure associated with vesicoureteral reflux. If the valvular incompetence resolves (and this is common), some degree of the hydronephrotic changes may persist. These persisting changes may cause the physician to suspect the presence of obstruction, which may lead to unnecessary surgery. A radioisotope renogram to assess ureteral drainage function can be performed to determine whether organic obstruction is present.
4. Only in unilateral hydronephrosis are the advanced stages of hydronephrotic atrophy seen. Eventually, the kidney is destroyed and appears as a thin-walled sac filled with clear fluid (water and electrolytes) or purulent fluid (Figure 12–6).

If obstruction is unilateral, the increased intrarenal pressure causes some suppression of renal function on that side. The closer the intrapelvic pressure approaches the glomerular filtration pressure (6–12 mm Hg), the less urine can be secreted. Glomerular filtration rate and renal plasma flow are reduced, concentrating power is gradually lost, and the urea:creatinine concentration ratio of urine from the hydronephrotic kidney is lower than that of urine from the normal kidney.

Hydronephrotic atrophy is an unusual type of pathologic change. Other secretory organs (eg, the submaxillary gland) cease secreting when their ducts are obstructed. This causes primary (disuse) atrophy. The completely obstructed kidney, however, continues to secrete urine. (If this were not so, hydronephrosis could not occur, since it depends on increased intrarenal pressure.) As urine is excreted into the renal pelvis, fluid and, particularly, soluble substances are reabsorbed, through either the tubules or the lymphatics. This has been demonstrated by injecting phenolsulfonphthalein (PSP) into the obstructed renal pelvis. It disappears (is reabsorbed) in a few hours and is excreted by the contralateral kidney. If the intrapelvic pressure in the hydronephrotic kidney rapidly increases to a level approaching filtration pressure (resulting in cessation of filtration), a safety mechanism is activated that produces a break in the surface lining of the collecting structure at the weakest point—the fornices. This leads to escape and extravasation of urine from the



▲ **Figure 12–6.** Pathogenesis of unilateral hydronephrosis. Progressive changes in ureter and kidney secondary to obstructing calculus (*arrowheads*). As the right kidney undergoes gradual destruction, the left kidney gradually enlarges (compensatory hypertrophy).

renal pelvis into the parenchymal interstitium (pyelointerstitial backflow). The extravasated fluid is absorbed by the renal lymphatics, and the pressure in the renal pelvis drops, allowing further filtration of urine. This explains the process by which the markedly hydronephrotic kidney continues to function. Further evidence of the occurrence of extravasation and reabsorption is that the markedly hydronephrotic kidney does not contain urine in the true sense; only water and a few salts are present.

Functional impairment in unilateral hydronephrosis, as measured by excretory urograms or renal scintagrams, is greater and increases more rapidly than that seen in bilateral hydronephrotic kidneys showing comparable damage on urography. As unilateral hydronephrosis progresses, the normal kidney undergoes compensatory hypertrophy (particularly in children) of its nephrons (renal counterbalance), thereby assuming the function of the diseased kidney in order to maintain normal total renal function. For this reason, successful anatomic repair of the ureteral obstruction of such a kidney may fail to improve its powers of waste elimination.

If both kidneys are equally hydronephrotic, a strong stimulus is continually being exerted on both to maintain maximum function. This is also true of a hydronephrotic solitary kidney. Consequently, the return of function in these kidneys after repair of their obstructions can be seen.

The extent of recovery after partial obstruction is difficult to determine preoperatively. Renal scanning with dimercaptosuccinic acid (DMSA) is most helpful. Temporary drainage, especially by nephrostomy, followed by tests to assess renal function is the best measure.

▶ Physiologic Explanation of Symptoms of Bladder Neck Obstruction

The following hypothesis has been proposed to explain the syndrome known as "prostatism," which occurs with progressive vesical obstruction:

> The bladder, like the heart, is a hollow muscular organ that receives fluid and forcefully expels it, and, like the heart, it reacts to an increasing workload by going through the successive phases of compensation and finally decompensation.
>
> Normally, contraction of the detrusor muscle in the presence of urine pulls the bladder neck open and the urine is expelled. The intravesical pressure generated in this instance varies between 20 and 40 cm of water.
>
> With bladder neck obstruction, hypertrophy of the vesical musculature develops, allowing the intravesical voiding pressure to rise to 50–100 cm or more of water in order to overcome the increased outlet resistance. Despite this compensation, the encroaching prostate appears to interfere with the mechanisms that ordinarily open the internal orifice. Also, the contraction phase may not last long enough for all the urine to be expelled; "exhaustion" of the muscle occurs prematurely. The refractory phase then sets in, and the detrusor is temporarily unable to respond to further stimuli. A few minutes later, voiding may be initiated again and completed.

A. Compensation Phase

1. Stage of irritability—In the earliest stages of obstruction of the bladder neck, the vesical musculature begins to hypertrophy. The force and size of the urinary stream remain normal because the balance is maintained between the expelling power of the bladder and urethral resistance. During this phase, however, the bladder appears to be hypersensitive. As the bladder is distended, the need to void is experienced. In patients with a normal bladder, these early urges can be inhibited, and the bladder relaxes and distends to receive more urine. However, in patients with a hypertrophied detrusor, the contraction of the detrusor is so strong that it virtually goes into spasm, producing the symptoms of an irritable bladder. The earliest symptoms of bladder neck obstruction, therefore, are urgency (even to the point of incontinence) and frequency, both day and night.

2. Stage of compensation—As the obstruction increases, further hypertrophy of the muscle fibers of the bladder occurs, and the power to empty the bladder completely is thereby maintained. During this period, in addition to urgency and frequency, the patient notices hesitancy in initiating urination while the bladder develops contractions strong enough to overcome resistance at the bladder neck. The obstruction causes some loss in the force and size of the urinary stream, and the stream becomes slower as vesical emptying nears completion (exhaustion of the detrusor as it nears the end of the contraction phase).

B. Decompensation Phase

If vesical tone becomes impaired or if urethral resistance exceeds detrusor power, some degree of decompensation occurs. The contraction phase of the vesical muscle becomes too short to completely expel the contents of the bladder, and some urine remains in the bladder (residual urine).

1. Acute decompensation—The tone of the compensated vesical muscle can be temporarily impaired by rapid filling of the bladder (high fluid intake) or by overstretching of the detrusor (postponement of urination although the urge is felt). This may cause increased difficulty of urination, with marked hesitancy and the need for straining to initiate urination; a very weak and small stream; and termination of the stream before the bladder completely empties (residual urine). Acute and sudden complete urinary retention also may occur.

2. Chronic decompensation—As the degree of obstruction increases, a progressive imbalance between the power of the bladder musculature and urethral resistance develops.

Therefore, it becomes increasingly difficult to expel all the urine during the contraction phase of the detrusor. The symptoms of obstruction become more marked. The amount of residual urine gradually increases, and this diminishes the functional capacity of the bladder. Progressive frequency of urination is noted. On occasion, as the bladder decompensates, it becomes overstretched and attenuated. It may contain 1000–3000 mL of urine. It loses its power of contraction, and overflow (paradoxic) incontinence results.

Clinical Findings

A. Symptoms

1. Lower and midtract (urethra and bladder)—Symptoms of obstruction of the lower and midtract are typified by the symptoms of urethral stricture, benign prostatic hyperplasia, neurogenic bladder, and tumor of the bladder involving the vesical neck. The principal symptoms are hesitancy in starting urination, lessened force and size of the stream, and terminal dribbling. Hematuria, which may be partial (eg, with stricture), initial or terminal (eg, with prostatic congestion), or total (eg, with vesical tumor), may occur. Other symptoms can include burning on urination, cloudy urine (due to complicating infection), and occasionally acute urinary retention (Elbadawi, 1998a,b).

2. Upper tract (ureter and kidney)—Symptoms of obstruction of the upper tract are typified by the symptoms of ureteral stricture or ureteral or renal stone. The principal complaints are pain in the flank radiating along the course of the ureter, gross hematuria (from stone), gastrointestinal symptoms, chills, fever, burning on urination, and cloudy urine with onset of infection, which is the common sequel to obstruction or vesicoureteral reflux. Nausea, vomiting, loss of appetite, weight and strength, and pallor are due to uremia secondary to bilateral hydronephrosis. A history of vesicoureteral reflux in childhood may be significant (Aslan and Kogan, 2003). Obstruction of the upper tract may be silent even when uremia supervenes.

B. Signs

1. Lower and midtract—Palpation of the urethra may reveal induration about a stricture. Rectal examination may show atony of the anal sphincter (damage to the sacral nerve roots) or benign or malignant enlargement of the prostate. Vesical distention may be found.

Although observation of the force and caliber of the urinary stream affords a rough estimate of maximum flow rate, the rate can be measured accurately with a urine flowmeter or, even more simply, by the following technique: Have the patient begin to void. When observed maximum flow has been reached, interpose a container to collect the urine and simultaneously start a stopwatch. After exactly 5 seconds, remove the container. The flow rate in milliliters per second can easily be calculated. The normal urine flow rate is 20–25 mL/s in males and 25–30 mL/s in females. Any flow rate <15 mL/s should be regarded with suspicion. A flow rate <10 mL/s is indicative of obstruction or weak detrusor function. Flow rates associated with an atonic neurogenic bladder (diminished detrusor power), or with urethral stricture or prostatic obstruction (increased urethral resistance), may be as low as 3–5 mL/s. A cystometrogram can differentiate between these two causes of impaired flow rate. After definitive treatment of the cause, the flow rate should return toward normal.

In the presence of a vesical diverticulum or vesicoureteral reflux, although detrusor power is normal, the urinary stream may be impaired because of the diffusion of intravesical pressure into the diverticulum and vesicoureteral junction as well as the urethra. Excision of the diverticulum or repair of the vesicoureteral junctions leads to efficient expulsion of urine via the urethra.

2. Upper tract—An enlarged kidney may be discovered by palpation or percussion or appreciated on radiographic imaging. Renal tenderness may be elicited if infection is present. Cancer of the cervix may be noted; it may invade the base of the bladder and occlude one or both ureteral orifices, or its metastases to the iliac lymph nodes may compress the ureters. A large pelvic mass (tumor, pregnancy) can displace and compress the ureters. Children with advanced urinary tract obstruction (usually due to posterior urethral valves) may develop ascites. Rupture of the renal fornices allows leakage of urine retroperitoneally; with rupture of the bladder, urine may pass into the peritoneal cavity through a tear in the peritoneum (Kibar et al, 2010).

C. Laboratory Findings

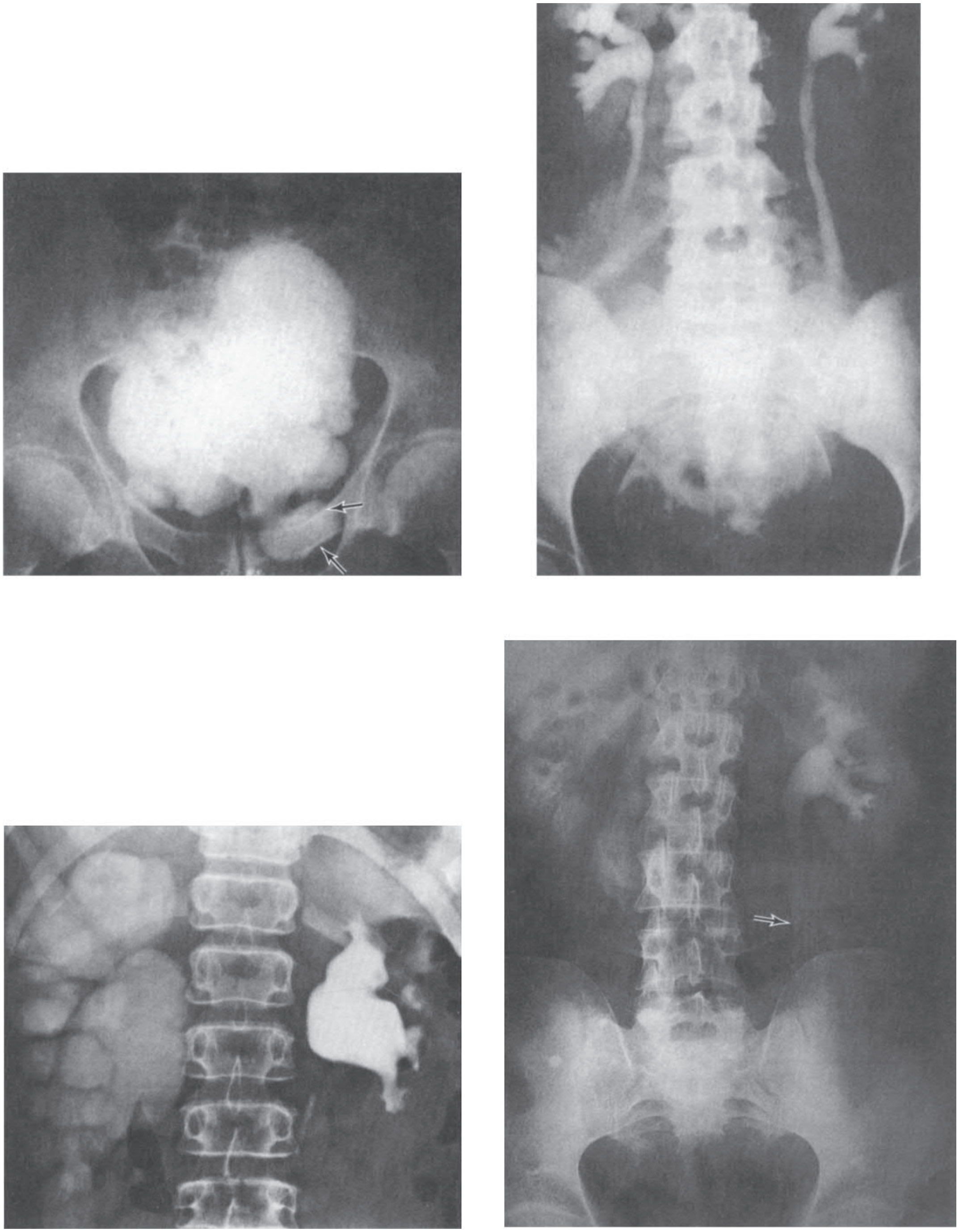
Anemia may be found secondary to chronic infection or in advanced bilateral hydronephrosis (stage of uremia). Leukocytosis is to be expected in the acute stage of infection. Little, if any, elevation of the white blood count accompanies the chronic stage.

Large amounts of protein seldom are found in the obstructive uropathies. Casts are not common from hydronephrotic kidneys. Microscopic hematuria may indicate renal or vesical infection, tumor, or stone. Evidence of purulent cells and bacteria may or may not be present. In the presence of significant bilateral hydronephrosis, both urea and creatinine are elevated.

D. Urinary Tract Imaging (Figure 12–7)

A plain film of the abdomen may show enlargement of renal shadows, calcific bodies suggesting ureteral or renal stone, or tumor metastases to the bones of the spine or pelvis. Metastases in the spine may be the cause of spinal cord damage (neuropathic bladder); if they are osteoblastic, they are almost certainly from cancer of the prostate.

Computerized tomography and excretory urograms reveal almost the entire story unless renal function is



▲ **Figure 12–7.** Changes in bladder, ureters, and kidneys caused by obstruction. ***Upper left:*** Cystogram showing benign prostatic enlargement and multiple diverticula. Arrows point to femoral hernia that probably developed as a result of straining to urinate. ***Upper right:*** Pregnancy. Significant dilatation and elongation of upper right ureter due to compression at the pelvic line. Left side normal. ***Lower left:*** Excretory urogram, 70 minutes after injection. Advanced right hydronephrosis secondary to ureteropelvic obstruction. Mild ureteropelvic obstruction on left. ***Lower right:*** Stone in left ureter (at *arrow*) with mild hydronephrosis.

severely impaired. They are more informative when partial obstruction is present because the radiopaque material is retained. These urograms demonstrate the degree of dilatation of the pelves, calyces, and ureters. The point of ureteral stenosis is frequently revealed. Segmental dilatation of the lower end of a ureter implies the possibility of vesicoureteral reflux (Figure 12–7), which can be appreciated by voiding cystography. The cystogram may show trabeculation as an irregularity of the vesical outline and may show diverticula. Vesical tumors, nonopaque stones, and large intravesical prostatic lobes may cause radiolucent shadows. A film taken immediately after voiding will show residual urine.

Retrograde cystography shows changes of the bladder wall caused by distal obstruction (trabeculation, diverticula) or demonstrates the obstructive lesion itself (enlarged prostate, posterior urethral valves, cancer of the bladder). If the ureterovesical valves are incompetent, ureteropyelograms may be obtained by reflux.

Retrograde urograms may show better detail than the excretory type, but care must be taken not to overdistend the passages with too much opaque fluid; small hydronephroses can be made to look quite large. The degree of ureteral or ureterovesical obstruction can be judged by the degree of delay of drainage of the radiopaque fluid instilled.

Computed tomography (CT), magnetic resonance imaging (MRI), and sonography can also help determine the extent of dilatation and parenchymal atrophy (Silverman et al, 2009). CT scan with and without contrast is the best modality when stone obstruction is suspected (Kennish et al, 2010). To avoid irradiation in pregnant women, MRI and sonography are the preferred tests. However, both tests have limited value in delineating ureteral anatomy if it is not dilated.

E. Isotope Scanning (Nuclear Renography)

The glomerular agent technetium-99m (Tc99m) **diethylenetriaminepentaacetic acid (DTPA)** and the tubular agent Tc99m **mercaptoacetyltriglycine (MAG3)** are most commonly used in the evaluation of obstruction. However, to predict functional recovery, **dimercaptosuccinic acid (DMSA)**, a cortical agent, has been shown to be superior to tubular selective agents DTPA or MAG3. In the presence of obstruction, the radioisotope renogram may show depression of both the vascular and secretory phases and a rising rather than a falling excretory phase due to retention of the isotope-containing urine in the renal pelvis. Furosemide is often given 20 minutes after the tracer is given to induce diuresis, which helps the interpretation of the clearance curve.

F. Instrumental Examination

Exploration of the urethra with a catheter or other instrument is a valuable diagnostic measure. Passage may be blocked by a stricture or tumor. Spasm of the external sphincter may make passage difficult. Passage of the catheter immediately after voiding allows estimation of the amount of residual urine in the bladder. Bladder ultrasound also can accurately measure the amount of postvoid residual urine and determine outlet obstruction (Housami et al, 2009). Residual urine is common in bladder neck obstruction (enlarged prostate), cystocele, and neurogenic (neuropathic) bladder.

Measurement of vesical tone by means of cystometry is helpful in diagnosing neurogenic bladder and in differentiating between bladder neck obstruction and vesical atony. Inspection of the urethra, bladder, ureter, and renal pelvis by means of panendoscopy, cystoscopy, or ureteroscopy may reveal the primary obstructive cause (Van Cangh et al, 2001). Catheters may be passed to the renal pelves and urine specimens obtained. The function of each kidney may be measured, and retrograde ureteropyelograms can be obtained (Whitaker and Buxton-Thomas, 1984).

DIAGNOSIS, MANAGEMENT, AND PROGNOSIS

Differential Diagnosis

A thorough examination usually leaves no doubt about the diagnosis. The differential diagnosis under these circumstances is rarely difficult. If seemingly simple infection does not respond to medical therapy, or if infection recurs, obstruction, a foreign body, or vesicoureteral reflux is the probable cause, and complete study of the urinary tract is indicated.

Complications

Stagnation of urine leads to infection, which then may spread throughout the entire urinary system. Once established, infection is difficult and at times impossible to eradicate, even after the obstruction has been relieved.

Often, the invading organisms are urea splitting (*Proteus*, *Pseudomonas*, *Providencia*, and *Klebsiella*), which causes the urine to become alkaline. Calcium salts precipitate and form bladder or kidney stones more easily in alkaline urine (pH >7.2). If both kidneys are affected, the result may be renal insufficiency. Secondary infection increases renal damage.

Pyonephrosis is the end stage of a severely infected and obstructed kidney. The kidney is functionless and filled with thick purulent liquid. At times, a plain film of the abdomen may show an air urogram caused by gas liberated by infecting organisms.

Treatment

A. Relief from Obstruction

Treatment of the main causes of obstruction and stasis (benign prostatic hyperplasia, cancer of the prostate, neurogenic bladder, ureteral stone, posterior urethral valves, and ureteral stenosis) is described in detail elsewhere in this book (Glassberg, 2001; Hashim and Abrams, 2010; Myers and McAninch, 2009).

1. Lower tract obstruction (distal to the bladder)—With patients in whom secondary renal or ureterovesical damage (reflux in the latter) is minimal or nonexistent, correction of the obstruction is sufficient. If significant reflux is demonstrated and does not subside spontaneously after relief of obstruction, surgical repair may be needed. Repair becomes imperative if there is considerable hydronephrosis in addition to reflux. Preliminary drainage of the bladder by an indwelling catheter or other means of diversion (eg, loop ureterostomy) is indicated in order to preserve and improve renal function. If, after a few months of drainage, reflux persists, the incompetent ureterovesical junction should be surgically repaired. Persistent obstruction from prostatic enlargement of urethral stricture also may require surgical intervention (Andrich and Mundy, 2008; Robert et al, 2011; Roehrborn, 2011).

2. Upper tract obstruction (above the bladder)—If tortuous, kinked, dilated, or atonic ureters have developed secondary to lower tract obstruction (so that they are themselves obstructive), vesical drainage will not protect the kidneys from further damage; the urine proximal to the obstruction must be diverted by nephrostomy or ureterostomy. Over a period of many months, the ureter may become less tortuous and less dilated; its obstructive areas may open. If radiopaque material instilled into the nephrostomy tube passes readily to the bladder, it may be possible to remove the nephrostomy tube. If obstruction or reflux persists, surgical repair is indicated. Permanent urinary diversion (eg, ureteroileal conduit) may be necessary.

If one kidney has been irreversibly damaged, as measured by kidney function tests, urography, sonography, CT scan, or scintigraphy, nephrectomy may be necessary.

B. Eradication of Infection

Once the obstruction is removed, every effort should be made to eradicate infection. If the infection has been severe and prolonged, antibiotics may fail to sterilize the urinary tract. On the other hand, the incidence of urinary tract infection is low in children whose upper tract obstruction is diagnosed prenatally (Roth et al, 2009).

▶ Prognosis

No simple statement about the prognosis in this group of patients would suffice. The outcome depends on the cause, site, degree, and duration of the obstruction. The prognosis is also definitely influenced by complicating infection, particularly if the infection has been present for a long time.

If renal function is fair to good, if the obstruction or other causes of stasis can be corrected, and if complicating infection can therefore be eradicated, the prognosis is generally excellent.

BIBLIOGRAPHY

Andrich DE, Mundy AR: What is the best technique for urethroplasty? Eur Urol 2008;54(5):1031–1041.

Aslan AR, Kogan BA: The effect of bladder outlet obstruction on the developing kidney. BJU Int 2003;92(Suppl 1):38.

Beganović A et al: Ectopic ureterocele: Long-term results of open surgical therapy in 54 patients. J Urol 2007;178(1):251–254.

Chevalier RL et al: Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. Pediatr Nephrol 2010;25(4):687–697.

Elbadawi A: Voiding dysfunction in benign prostatic hyperplasia: Trends, controversies and recent revelations. I. Symptoms and urodynamics. Urology 1998a;51(Suppl 5A):62.

Elbadawi A: Voiding dysfunction in benign prostatic hyperplasia: Trends, controversies and recent revelations. II. Pathology and pathophysiology. Urology 1998b;51(Suppl 5A):73.

Gimpel C et al: Complications and long-term outcome of primary obstructive megaureter in childhood. Pediatr Nephrol 2010;25(9):1679–1686.

Glassberg KI: The valve bladder syndrome: 20 years later. J Urol 2001;166:1406.

Hashim H, Abrams P: Emerging drugs for the treatment of benign prostatic obstruction. Expert Opin Emerg Drugs 2010;15(2):159–174.

Housami F et al: The use of ultrasound-estimated bladder weight in diagnosing bladder outlet obstruction and detrusor overactivity in men with lower urinary tract symptoms. Indian J Urol 2009;25(1):105–109.

Kennish SJ et al: Unenhanced CT for the evaluation of acute ureteric colic: The essential pictorial guide. Postgrad Med J 2010;86(1017):428–436.

Kibar Y et al: Timing of posterior urethral valve diagnosis and its impact on clinical outcome. J Pediatr Urol 2010;7(5):538–842.

Klein J et al: Congenital ureteropelvic junction obstruction: Human disease and animal models. Int J Exp Pathol 2010;92(3): 168–192.

Lieber MM et al: Natural history of benign prostatic enlargement: Long-term longitudinal population-based study of prostate volume doubling times. BJU Int 2010;105(2):214–219.

Myers JB, McAninch JW: Management of posterior urethral disruption injuries. Nat Clin Pract Urol 2009;6(3):154–163.

Riccabona M: Obstructive diseases of the urinary tract in children: Lessons from the last 15 years. Pediatr Radiol 2010;40(6):947–955.

Robert G et al: Lower urinary tract symptoms suggestive of benign prostatic hyperplasia: Who are the high-risk patients and what are the best treatment options? Curr Opin Urol 2011;21(1): 42–48.

Rodriguez MM: Developmental renal pathology: Its past, present, and future. Fetal Pediatr Pathol 2004;23:211.

Roehrborn CG: Male lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). Med Clin North Am 2011;95(1):87–100.

Roth CC et al: Occurrence of urinary tract infection in children with significant upper urinary tract obstruction. Urology 2009; 73(1):74–78.

Routh JC et al: Predicting renal outcomes in children with anterior urethral valves: A systematic review. J Urol 2010;184(4 Suppl): 1615–1619.

Silverman SG et al: What is the current role of CT urography and MR urography in the evaluation of the urinary tract? Radiology 2009;250(2):309–323.

Tan BJ, Smith AD: Ureteropelvic junction obstruction repair: When, how, what? Curr Opin Urol 2004;14:55.

Tanagho EA, Meyers FH: Trigonal hypertrophy: A cause of ureteral obstruction. J Urol 1965;93:678.

Van Cangh PJ et al: The role of endourology in ureteropelvic junction obstruction. Curr Urol Rep 2001;2:149.

Vecchioli-Scaldazza C, Morosetti C: Effect of aging on urinary incontinence in woman. Arch Ital Urol Androl 2010;82(3):167–171.

Whitaker RH, Buxton-Thomas M: A comparison of pressure flow studies and renography in equivocal upper urinary tract obstruction. J Urol 1984;131:446.

This page intentionally left blank

Vesicoureteral Reflux

13

Thomas W. Gaither, MD, MAS; & Hillary L. Copp, MD, MS

Under normal circumstances, the ureterovesical junction allows urine to enter the bladder but prevents urine from regurgitating into the ureter, particularly at the time of voiding. In this way, the kidney is protected from high pressure in the bladder and from contamination by infected vesical urine. When this valve is incompetent, the chance for development of urinary infection is significantly enhanced, and pyelonephritis may occur.

ANATOMY OF THE URETEROVESICAL JUNCTION

An understanding of the causes of vesicoureteral reflux (VUR) requires knowledge of the anatomy of the ureterovesical junction. Anatomic studies performed by Hutch (1972) and Tanagho and Pugh (1963) (Figure 13–1) are incorporated into the following discussion.

Mesodermal Components

The mesodermal component, which arises from the Wolffian duct, is made up of two parts that are innervated by the sympathetic nervous system.

A. The Ureter and the Superficial Trigone

The smooth musculature of the renal calyces, pelvis, and extravesical ureter is composed of helically oriented fibers that allow for peristaltic activity. As these fibers approach the vesical wall, they are reoriented into the longitudinal plane. The ureter passes obliquely through the vesical wall; the intravesical ureteral segment is thus composed of longitudinal muscle fibers only and therefore cannot undergo peristalsis. As these smooth-muscle fibers approach the ureteral orifice, those that form the roof of the ureter swing to either side to join those that form its floor. They then spread out and join equivalent muscle bundles from the other ureter and continue caudally, thus forming the superficial trigone. The trigone passes over the neck of the bladder, ending at the verumontanum in the male and just inside the external urethral meatus in the female. Thus, the ureterotrigonal complex is one structure. Above the ureteral orifice, it is tubular; below that point, it is flat.

B. Waldeyer's Sheath and the Deep Trigone

Beginning at a point about 2–3 cm above the bladder, an external layer of longitudinal smooth muscle surrounds the ureter. This muscular sheath passes through the vesical wall, to which it is connected by a few detrusor fibers. As it enters the vesical lumen, its roof fibers diverge to join its floor fibers, which then spread out, joining muscle bundles from the contralateral ureter and forming the deep trigone, which ends at the bladder neck. Ureteric nerves occupy the medial aspect of the distal ureter, and completely encircle the ureter at the ureterovesical junction. The nerves travel just outside Waldeyer's sheath (Yucel and Baskin, 2003).

Endodermal Component

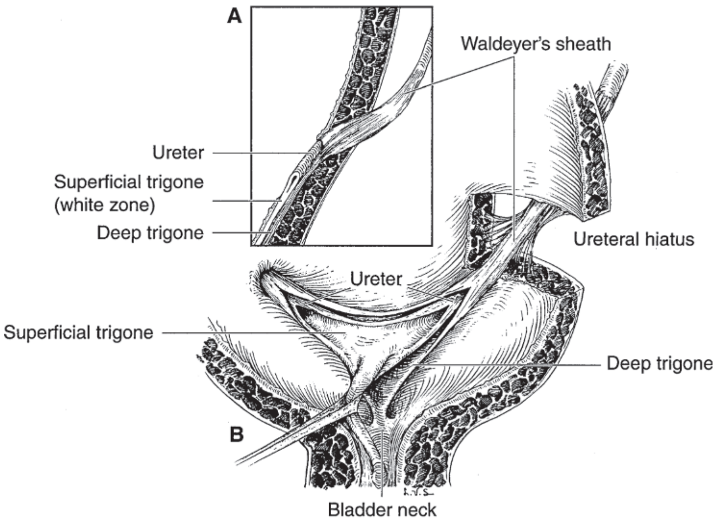
The vesical detrusor muscle bundles are intertwined and run in various directions. As they converge on the internal orifice of the bladder, however, they tend to become oriented into three layers.

A. Internal Longitudinal Layer

The internal longitudinal layer continues into the urethra submucosally and ends just inside the external meatus in the female and at the caudal end of the prostate in the male.

B. Middle Circular Layer

The middle circular layer is thickest anteriorly and stops at the vesical neck.



The ureteral muscle extends downward and becomes the superficial trigone.

Waldeyer's sheath extends downward and becomes the deep trigone.

▲ **Figure 13–1.** Normal ureterotrigonal complex. ***A:*** Side view of ureterovesical junction. Waldeyer's muscular sheath invests the juxtavesical ureter and continues downward as the deep trigone, which extends to the bladder neck. The ureteral musculature becomes the superficial trigone, which extends to the verumontanum in the male and stops just short of the external meatus in the female. ***B:*** Waldeyer's sheath is connected by a few fibers to the detrusor muscle in the ureteral hiatus. This muscular sheath, inferior to the ureteral orifices, becomes the deep trigone. The musculature of the ureters continues downward as the superficial trigone.

C. Outer Longitudinal Layer

The muscle bundles of the outer longitudinal layer take a circular and spiral course about the external surface of the female urethra and are incorporated within the peripheral prostatic tissue in the male. They constitute the true vesicourethral sphincter. The vesical detrusor muscle is innervated by the parasympathetic nerves (S_2–S_4).

PHYSIOLOGY OF THE URETEROVESICAL JUNCTION

There are competing theories to explain the cause of primary VUR. Work by Tanagho and colleagues supports the assumption that primary reflux is due to a marked deficiency in the development of the ureterotrigonal musculature that prevents occlusion of the intravesical ureter and permits VUR. Others believe that reflux is due primarily to an anatomical deficiency of the ureterovesical junction (UVJ), as those with reflux have shorter intravesicular ureteral lengths (Paquin, 1959). Abnormalities in neural function and architecture may also contribute to reflux (Oswald et al, 2004).

GENETICS OF VESICOURETERAL REFLUX

There appears to be genetic predisposition for reflux. The reported prevalence of VUR among siblings of index patients with reflux is 27.4 (2.9–51.9)%, which is significantly higher than the incidence of reflux in the general population (1%) (Skoog et al, 2010). Severe reflux may be inherited in an X-linked dominant fashion (Naseri et al, 2010). In addition, the incidence of reflux varies among nationalities and races. Studies involving genotype screening of specific subgroups of patients suggest that there is heterogeneity in the genetics of VUR (reviewed by Carvas et al, 2010). Several genes have been associated with VUR, including uroplakin-3, SLIT2/ROBO2, and TGF-β. In addition, several chromosomal regions (on chromosomes 1, 2, 3, 5, 13, 18, and 23) have also been identified. Despite extensive analysis, the exact form of genetic transmission has yet to be delineated.

VESICOURETERAL REFLUX CAUSES

The causes of VUR are generally separated into two categories: primary and secondary. Primary reflux is due to the anatomical deficiencies of the UVJ mentioned above. In primary reflux, the structures outside of the UVJ are otherwise normal. Secondary reflux occurs when a hostile bladder environment renders the normal UVJ incompetent. Often with treatment of the underlying cause (ie, relief of bladder outlet obstruction), the reflux will resolve.

Primary Reflux

A. Congenital UVJ Incompetence

Congenital UVJ incompetence is an anatomical deficiency leading to discordant trigone-induced closure of the UVJ. It is most often seen in young children, more commonly in girls than in boys. Reflux in adults—usually women—may represent the same congenital defect.

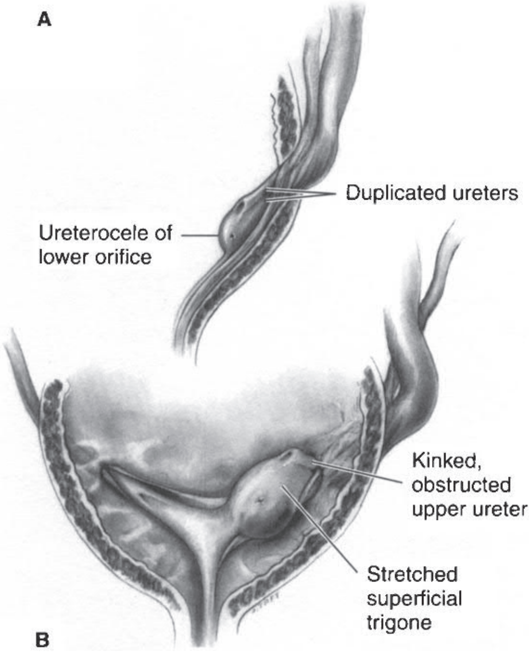
It is postulated that congenital UVJ incompetence is related to development of the ureteral bud on the mesonephric duct. It is known that the ureter acquires its musculature from its cranial end caudally so that if a segment is muscularly deficient, it is deficient in its most caudal part. It is also postulated that if the ureter is too close to the urogenital sinus on the mesonephric duct, it will join the latter relatively early in embryonic life, before acquiring adequate mesenchymal tissue around itself to be differentiated later into proper trigonal musculature as well as lower ureter. This embryologic hypothesis explains all the known features of refluxing ureters: their muscular weakness, their lateral placement on the bladder base with a very short submucosal segment, and their usual association with weak ureteral musculature and gaping ureteral orifices (which, in severe cases, ensures a golfhole endoscopic appearance at their junction with the bladder wall). It also explains why, in duplicated systems, if there is only one refluxing unit, it is the superolateral orifice from the lower pole moiety (which originated closer to the urogenital sinus on the mesonephric duct and thus has the least muscular development) (see Figure 13–2).

B. Ureteral Abnormalities

1. Complete ureteral duplication (Figure 13–3)—The intravesical portion of the ureter to the upper renal segment is usually of normal length, whereas that of the ureter to the lower pole is abnormally short; this orifice is commonly incompetent. Also, Stephens (1957) demonstrated that the musculature of the superiorly placed orifice is attenuated, which further contributes to its weakness.

2. Ectopic ureteral orifice—A single ureter or one of a pair may open well down on the trigone, at the vesical neck, or in the urethra. Such intravesical ureteral segments are usually devoid of smooth muscle. Thus, they have no occlusive force and VUR is the rule.

3. Ureterocele—A ureterocele involving a single ureter rarely allows reflux, but ureteroceles are more commonly associated with the upper pole ureter of a duplicated kidney. Because the ureterocele orifice is obstructed, the more proximal intramural ureter becomes dilated. This increases the diameter of the muscular hiatus, where the ureters of the duplicated system enter the bladder, further shortening the intravesical segment of the associated lower pole ureter, which therefore may become incompetent.


A
Duplicated ureters
Ureterocele of lower orifice
Kinked, obstructed upper ureter
Stretched superficial trigone
B

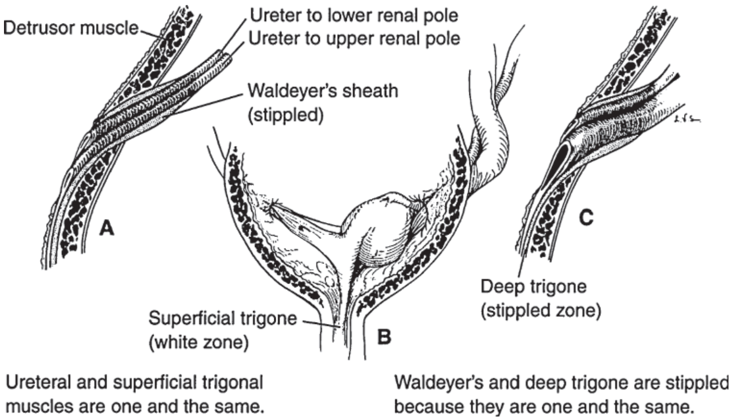
▲ **Figure 13–2.** ***A:*** Orifice of lower pole moiety in duplicated system is located superolaterally along trigone and prone to reflux. ***B:*** Ureterocele orifice located inferomedially and associated with upper pole moiety of duplicated system (diagrammatic representation). (Reproduced with permission from Tanagho EA: Ureteroceles: Embryogenesis, pathogenesis and management, J Cont Educ Urol. 1979;Feb;6(1)18:13.)

Secondary Reflux

A. Bladder and Bowel Dysfunction

Abnormal voiding habits have been associated with reflux. Toilet-trained children, especially girls, may alter their bladder function by inhibiting their urge to void. This can result in abnormally high voiding pressure, bladder overactivity, and poor bladder compliance. These changes in bladder dynamics can either induce the development of reflux or prevent its resolution (Greenfield and Wan, 2000).

Alterations in the bowel function (eg, constipation) can cause further deterioration in bladder function and consequently the development or persistence of primary reflux (Bower et al, 2005). The combination of functional constipation and lower urinary tract symptoms has been recently


Detrusor muscle
Ureter to lower renal pole
Ureter to upper renal pole
Waldeyer's sheath
(stippled)
A
B
C
Deep trigone
(stippled zone)
Superficial trigone
(white zone)
Ureteral and superficial trigonal
muscles are one and the same.
Waldeyer's and deep trigone are stippled
because they are one and the same.

▲ **Figure 13–3.** Ureteral duplication and ureterocele as causes of vesicoureteral reflux. ***A:*** Ureteral duplication showing juxtavesical and intravesical ureters encased in common sheath (Waldeyer's). The superior ureter, which always drains the lower renal pole, has a shorter intravesical segment; in addition, it is somewhat devoid of muscle. It therefore tends to allow reflux. ***B:*** Duplication with ureterocele that always involves caudal ureter, which drains the upper renal pole. Pinpoint orifice is obstructive, causing hydroureteronephrosis. Resulting wide dilatation of ureter and ureteral hiatus shortens the intravesical segment of the other ureter, often causing it to reflux. ***C:*** Resection of ureterocele allows reflux into that ureter.

termed bladder and bowel dysfunction (BBD) (Burgers et al, 2013) (Peters et al, 2010). BBD has been associated with reflux, and children with both BBD and VUR have lower likelihood of VUR resolution. (Peters et al, 2010). Children with both reflux and BBD are one of groups at highest risk for urinary tract infections (UTIs) (Keren et al, 2015).

B. High-Pressure Voiding

Occasionally, a heavily trabeculated bladder may be associated with reflux. The causes include neurogenic bladder and severe obstruction distal to the bladder. A bladder that is contracted secondary to various causes, including interstitial cystitis, tuberculosis, radiotherapy, carcinoma, or schistosomiasis, may also have ureteral reflux due to high-pressure voiding.

Hostile Bladder Secondary to Cystitis

A "borderline" ureterovesical junction may not allow reflux when the urine is sterile, but valvular function may be impaired when cystitis causes associated edema involving the trigone and intravesical ureter. In addition, the abnormally high voiding pressure may lead to reflux, in which case, secondary pyelonephritis may ensue. After cure of the infection, cystography again reveals no reflux. It is believed that a completely normal junction will not decompensate even under these circumstances.

Patients with a history of VUR and childhood UTIs may have increased morbidity during pregnancy, including episodes of bacteriuria and pyelonephritis (Martinell et al, 1990). The pathophysiology of reflux during pregnancy is unclear. This condition may be aggravated by the hormones of pregnancy, which may contribute to a further loss of tone of the ureterotrigonal complex. After delivery, reflux is usually no longer demonstrable (Hutch and Amar, 1972).

Prune Belly Syndrome

"Prune belly" syndrome is a relatively rare condition in which there is bilateral cryptorchidism and failure of normal development of the abdominal muscles and the smooth muscle of the ureters and bladder. Because the smooth muscle of the ureterotrigonal complex is deficient, reflux is common.

Iatrogenic Causes

Certain operative procedures may lead to either temporary or permanent ureteral regurgitation.

A. Ureteral Meatotomy

Extensive ureteral meatotomy may be followed by reflux. Fortunately, however, limited incision of the roof of the intravesical ureter divides few muscle fibers. Wide resection for treatment of vesical cancer or UVJ stone removal may be followed by ureteral reflux.

B. Puncture/Resection of Ureterocele

If the ureteral hiatus is widely dilated, ureterocele puncture is often followed by reflux in the punctured ureter in approximately half of cases (Chertin et al, 2003). Because ureteroceles are often a part of a duplicated system, ureterocele puncture can also cause de novo reflux of the previously nonrefluxing lower pole ureter or even the contralateral ureter due to disruption of trigonal support (Jesus et al, 2011). Ureteroceles often lack muscular backing. Therefore, formal ureterocele resection with ureteral reimplantation may be required if reflux is occurring in the ipsilateral lower pole moiety or contralateral side.

COMPLICATIONS

Dilation of the ureter, renal pelvis, and calyces is usually observed in association with reflux, sometimes to an extreme degree, and is termed **hydroureteronephrosis**. In males, because they have a relatively long segment of sterile urethra, such changes are often seen in the absence of infection.

In the prenatal setting, high-grade VUR may be associated with small kidneys and cortical abnormalities. Whether VUR causes these kidney abnormalities or whether malformation of the kidney leads to VUR is a subject of controversy. After the prenatal period, refluxing sterile urine is not believed to cause renal damage. Recent mouse models have shown that sterile reflux alone fails to induce reflux nephropathy (Bowen et al, 2013). Additionally, children with documented VUR without febrile UTIs are not at an increased risk for renal scarring (Al-Sayyad et al, 2005). However, infected refluxing urine may cause renal scarring.

The cycling of urine caused by VUR can create persistent residual urine and counteracts one of the body's natural UTI defense mechanisms of regular emptying, which prohibits accumulation of bacteria within the urinary tract. Moreover, reflux may increase the risk that infected urine within the bladder may reach the kidney, converting cystitis to pyelonephritis (see also Chapter 14). Additionally, persistent residual urine that is infected may be difficult to clear. Regardless, in children with a first-time febrile UTI, VUR is present in approximately 40% of cases (Hoberman et al, 2003). VUR is a risk factor for recurrent UTIs (Keren et al, 2015).

EPIDEMIOLOGY

Vesicoureteral reflux occurs in 25–40% (Fanos and Cataldi, 2004; Hoberman et al, 2003) of children with UTI but in only 8% of adults with bacteriuria. The true prevalence of VUR in adults is most likely underestimated since VCUGs are not routinely performed in this population. In screening populations, VUR is estimated to be about 27% in siblings and 36% in offspring (Skoog et al, 2010). Screening for VUR in siblings and offspring of patients with known VUR is recommended if there is evidence of renal cortical abnormalities or renal size asymmetry on ultrasound or if there is a history of a UTI (Skoog et al, 2010).

When infection associated with reflux occurs during the first few weeks of life, many patients are septic and uremic. After 1 year of age, females are twice as likely to be found to have VUR compared to males (Chand et al, 2003). However, this finding is likely due to increased screening in females due to a higher incidence of UTI (Foxman, 2002).

CLINICAL FINDINGS

▶ Signs and Symptoms

Patients typically present in one of two ways: as a result of prenatal hydronephrosis or a UTI. Otherwise, VUR is an asymptomatic disease. Here we review the clinical findings of patients with presumed VUR. In infants, UTI may present with fever or nonspecific signs such as failure to thrive, vomiting, diarrhea, poor oral intake, or lethargy. In older children, the usual symptoms are chills and high fever, flank pain, nausea and vomiting, and/or lower urinary tract symptoms such as dysuria, hematuria, urgency, or incontinence.

▶ Physical Exam

In primary reflux without signs of infection, the physical exam is normal. During an attack of febrile UTI/acute pyelonephritis, suprapubic and/or costovertebral angle tenderness may be noted. Findings associated with secondary causes of VUR should be noted. All male infants and young children should be assessed for phimosis, as uncircumcised male infants have a 10-fold higher incidence of febrile UTI compared to circumcised infants (Singh-Grewal et al, 2005). Palpation and percussion of the suprapubic area may reveal a distended bladder secondary to distal obstruction or neurogenic disease. Spinal abnormalities such as a sacral dimple may be a sign of spina bifida. All patients with VUR should be assessed for hypertension, although this finding may not be an issue until well into adulthood.

▶ Laboratory Findings

Routine monitoring of urine for infection is not recommended unless the patient has signs and symptoms of a UTI. Yearly urinalysis should be monitored for protein. The serum creatinine may be elevated in the advanced stage of renal damage, but it may be normal even when the degree of reflux and hydronephrosis is marked. A baseline creatinine should be drawn, and if elevated, should prompt functional renal imaging (Peters et al, 2010).

▶ Imaging

Imaging is the mainstay of screening and diagnosing VUR.

A. Renal Bladder Ultrasound

Renal bladder ultrasound (RBUS) is the most common imaging modality to evaluate the urinary tract in children. All children under the age of 2 years with a febrile UTI should be evaluated with a RBUS. Patients with any abnormalities on the ultrasound, including urinary tract dilation, should undergo formal testing for VUR (VCUG; see discussion below) (Roberts et al, 2010). RBUS are often used as an adjunctive technique to monitor renal growth and hydronephrosis grade.

B. Abdominal X-Ray Findings

An abdominal x-ray is not routinely performed in patients with suspected VUR; however, it may be useful in patients with suspected secondary reflux. In patients with BBD, a plain film may be used to access degree of constipation. The plain film may reveal evidence of spina bifida, meningomyelocele, or the absence of the sacrum and thus point to a neurologic deficit.

C. Voiding Cystourethrogram

The diagnostic gold standard of choice for VUR is the contrast voiding cystourethrogram (VCUG). The VCUG is a radiologic study that uses liquid contrast and an x-ray to evaluate the structure and function of the urinary system. Two main types of VCUG are widely used: fluoroscopic and radionuclide. Fluoroscopic VCUG carries a larger radiation burden and is often reserved for the initial diagnostic evaluation as it provides more anatomic detail. Radionuclide VCUG contains less radiation but provides less anatomic detail and is often used to monitor reflux over time. The international VUR grading system, first adopted in 1985, classifies reflux identified on fluoroscopic VCUG into five categories (see Figure 13–4). Reflux grade (grades I–V) directly correlates with the degree of valve incompetence. Although this grading system is widely used, the interrater reliability for moderate reflux is poor, suggesting a need for modification (Metcalfe et al, 2012). Additionally, false-negative VCUGs are common, and thus a second voiding cycle image is recommended if no reflux is found during the first voiding cycle (Neel et al, 2000).

In general, reflux demonstrable only with voiding implies a more competent valve than does reflux that occurs at low pressures. Failure to demonstrate reflux on one study does not rule out intermittent reflux that may occur only in the setting of infection.

TREATMENT

Conservative medical therapy is the mainstay of treatment, although surgery may be required in select cases. Goals of treatment include prevention of recurrent UTIs, pyelonephritis, and long-term sequelae such as hypertension and reflux nephropathy.

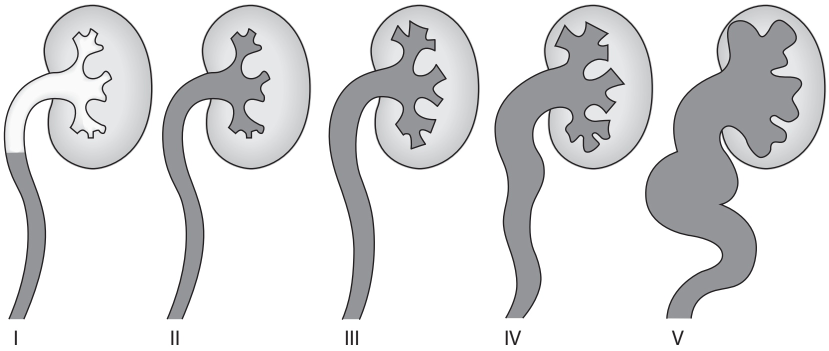
Medical Treatment

A. Indications

In most cases, children with primary reflux are initially treated medically, since there is a chance of spontaneous resolution. Positive predictors for reflux resolution include unilateral reflux, the lower grades of reflux, the earlier age of presentation, and male gender (Estrada et al, 2009). Larger bladder volumes at onset of reflux have also been associated with reflux resolution and may be an additional prognostic factor (Alexander et al, 2015). A boy with posterior urethral valves may cease to have reflux once these valves are destroyed.

B. Methods of Treatment

Urinary infection should be definitively treated with antimicrobial drugs, after which chronic suppressive therapy may be considered. The effectiveness of prophylactic antibiotics in the treatment of children with VUR is still



▲ **Figure 13–4.** Vesicoureteral reflux grade I—urine backs into ureter only; grade II—urine backs into ureter, renal pelvis, and calyces; grade III—same as grade II, but renal pelvis begins to look dilated and calyces are mildly blunted; grade IV—renal pelvis and calyces appear moderately dilated and blunted, respectively; grade V—ureter appears tortuous. (Reproduced with permission from Gargollo PC, Diamond DA: Therapy insight: What nephrologists need to know about primary vesicoureteral reflux, Nat Clin Pract Nephrol. 2007 Oct;3(10):551–563.)

controversial. Eight randomized controlled trials assessing the efficacy of antibiotic prophylaxis have been conducted in patients with primary VUR. In sum, continuous antibiotic prophylaxis reduces the risk of febrile and symptomatic UTIs with mixed evidence on the prevention of renal scarring (Wang et al, 2015). Although the risk of UTIs is decreased, patients on continuous antbiotic prophylaxis are at significant increased risk for antibiotic resistant bacteria. Continued research in risk stratification is necessary to determine which patients will gain the most benefit.

Children with primary VUR and bladder and bowel dysfunction are at high risk for UTIs. Management of the underlying bladder and bowel dysfunction is imperative, which includes behavioral therapy, biofeedback, anticholinergic medication, and treatment of the underlying constipation with laxatives. Optimal medical management is preferred before any surgical intervention for the VUR is undertaken.

C. Evaluation of Success of Medical Treatment

Cystograms should not be repeated any more frequently than every 12–18 months. If a patient has been infection-free for this time period, it is reasonable to stop the antibiotic prophylaxis and postpone imaging. RBUS should be performed periodically to ensure that renal deterioration does not occur. Nuclear renal scans may be used to determine the full extent of scarring if RBUS shows abnormalities. Spontaneous resolution is dependent on reflux grade. Resolution rates over 5 years by grade are: 90%, 70%, 50%, 30%, and 10% for grades I, II, III, IV, and V, respectively (see Figure 13–4) (Elder et al, 1997).

▶ Surgical Treatment

A. Indications

Surgery is indicated when medical therapy fails. Such indications include recurrent UTIs or pyelonephritis, medical nonadherence, and breakthrough infections by resistant organisms.

B. Types of Surgical Treatment

1. Temporary urinary diversion—Patients, typically infants, with high-grade VUR and recurrent infection may benefit from temporary urinary diversion by vesicostomy. This allows for somatic growth with bladder enlargement and improved anatomical parameters to maximize the success of ultimate ureteral reimplantation. If the ureters are dilated and kinked, a low redundant loop or end ureterostomy can be brought to the skin. The ureter can drain directly into the diaper. Later, the temporary diversion can be taken down and the ureter reimplanted into the bladder. Temporary diversion often is associated with a decrease in ureteral dilation and potentially helps to avoid having to taper the ureter at the time of definitive surgery.

2. Ureteral reimplantation

A. PRINCIPLES OF REPAIR—The goal of ureteral reimplantation is to construct a submucosal tunnel with a length 3–5 times the diameter of the ureter. Ureteral reimplantation may be performed via open or robot-assisted laparoscopic surgery. There are two main approaches—intravesical and extravesical—and each approach has various described techniques. The common steps of an intravesical approach include the following: (1) make a vertical incision in the bladder to gain access to the ureter(s), (2) incise the mucosa around the ureteral orifice, (3) dissect and mobilize the intravesical ureter from its attachments to Waldeyer's sheath, (4) create a submucosal tunnel, (5) place the ureter within the tunnel, (6) anastomose the ureteral orifice to the bladder mucosa, and (7) close any remaining mucosal defects within the bladder.

The main steps of an extravesical reimplant include (1) identify and dissect the ureter down to its anastomosis with the bladder, (2) separate the intramural portion of the ureter from the detrusor muscle, (3) divide the detrusor muscle down to the subepithelium to create a ~3-cm trough in which the ureter will lay, (4) mobilize the lateral flaps of the detrusor muscle for space for the ureter within the trough, and (5) close the bladder muscle with absorbable sutures over the ureter to create the tunnel.

B. RESULTS OF URETERAL REIMPLANTATION—About 95–100% of patients no longer show reflux after open surgical repair. Robotic assisted laparoscopic ureteral reimplantation may offer similar success rates, but further research is necessary (Marchini et al, 2011). Complications of reimplantation include ureterovesical stenosis (~3%) and persistent, contralateral low-grade reflux (~9%) (Sung and Skoog, 2012).

3. Endoscopic Treatment—Endoscopic treatment of reflux has become popular treatment for reflux. A biocompatible material such as Deflux (a mixture of dextranomer microspheres and non-animal-stabilized hyaluronic acid) can be injected into the intramural ureter. The bulking agent allows for the coaptation of the ureteral orifice and intramural ureter (Aaronson, 2005) in order to prevent reflux. The success rate for the subureteric transurethral injection (STING) approach varies from 70% to 90%, depending on the grade of the reflux treated, and decreases with subsequent STING procedures (Dogan et al, 2015). While it does not approximate the cure rate from open surgery, technical improvements and risk factors for failure are gradually being identified that are aimed at improving performance (reviewed by Routh et al, 2010). More recent studies have suggested that VUR may recur following successful endoscopic injection, warranting long-term follow-up (Yucel et al, 2007; Holmdahl et al, 2010). Overtime the approach to injection has evolved from the STING to the double hydrodistention implantation technique (double HIT). This technique delivers two intramural injections creating ureteral tunnel and orifice coaptation with improved success rates matching the success of open surgery in some series (Kalisvaart et al, 2012). Patient selection is an important aspect of procedure success rates, as the rate of cure with endoscopic therapy is less in children with versus without BBD; however, there is no difference in success rates for open surgery in children BBD (Skoog et al, 2010).

PROGNOSIS AND COMPLICATIONS

Long-term complications from VUR include hypertension and reflux nephropathy. The exact incidence of hypertension in patients with VUR is difficult to determine, although it appears to be related to the development of renal scarring and the degree of reflux (Fidan et al, 2013). The etiology of reflux nephropathy is thought to occur from two distinct mechanisms. Prenatal damage from reflux disrupts kidney development and can lead to renal dysplasia. Acquired reflux nephropathy can occur after multiple episodes of UTIs or pyelonephritis (Peters et al, 2010). However, the long-term danger of recurrent UTIs in children is questioned. In a large study of 1576 patients with chronic kidney disease (CKD), recurrent UTIs in childhood was possibly the cause of 1 case (0.3%) (Salo et al, 2011).

BIBLIOGRAPHY

Aaronson IA: Does deflux alter the paradigm for the management of children with vesicoureteral reflux? Curr Urol Rep 2005;6(2):152–156.

Alexander SE et al: Bladder volume at onset of vesicoureteral reflux is an independent risk factor for breakthrough febrile urinary tract infection. J Urol 2015:194(4):1342-1346.

Al-Sayyad AJ et al: Can prophylactic antibiotics safely be discontinued in children with vesicoureteral reflux? J Urol 2005;174(4):1587-1589.

Bowen SE et al: Interplay between vesicoureteral reflux and kidney infection in the development of reflux nephropathy in mice. Dis Model Mech 2013;6(4):934-941.

Bower WF et al: Dysfunctional elimination symptoms in childhood and adulthood. J Urol 2005;174(4, Pt 2):1623–1627; discussion 1627–1628.

Burgers RE et al: Management of functional constipation in children with lower urinary tract symptoms: report from the Standardization Committee of the International Children's Continence Society. J Urol 2013;190(1):29–36.

Carvas F et al: The genetics of primary, nonsyndromic vesicoureteral reflux. Curr Opin Urol 2010;20:336–342.

Chand DH et al: Incidence and severity of vesicoureteral reflux in children related to age, gender, race, and diagnosis. J Urol 2003;170(4):1548–1550.

Chertin B et al: Is primary endoscopic puncture of ureterocele a long-term effective procedure? J Pediatr Surg 2003;38(1):116–119.

Dogan HS et al: Factors affecting the success of endoscopic treatment of vesicoureteral reflux and comparison of two dextranomer based bulking agents: Does bulking substance matter? J Pediatr Urol 2015;11(2):e1–e5.

Elder JS et al: Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997;157(5):1846–1851.

Estrada CR Jr et al: Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: Results from 2462 children. J Urol 2009;182(4):1535–1541.

Fanos V, Cataldi L: Antibiotics or surgery for vesicoureteric reflux in children. Lancet 2004;364(9446):1720–1722.

Fidan K et al: Hypertension in pediatric patients with renal scarring in association with vesicoureteral reflux. Urology 2013;81(1):173–177.

Foxman B. Epidemiology of urinary tract infections: Incidence, morbidity, and economic costs. Am J Med 2002;113:5S-13S.

Gargollo PC, Diamond DA: Therapy insight: what nephrologists need to know about primary vesicoureteral reflux. Nat Clin Pract Nephrol 2007;3(10):551–563.

Greenfield SP, Wan J: The relationship between dysfunctional voiding and congenital vesicoureteral reflux. Curr Opin Urol 2000;10(6):607–610.

Hoberman A et al: Imaging studies after a first febrile urinary tract infection in young children. New Engl J Med 2003;348(3):195–202.

Holmdahl G et al: The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol 2010;184(1):280–285.

Hutch JA: The mesodermal component: Its embryology, anatomy, physiology and role in prevention of vesicoureteral reflux. J Urol 1972;108:406.

Hutch JA, Amar AD: Vesicoureteral Reflux and Pyelonephritis. Appleton-Century-Crofts, New York, 1972.

Jesus LE et al: Clinical evolution of vesicoureteral reflux following endoscopic puncture in children with duplex system ureteroceles. J Urol 2011;186(4):1455–1458.

Kalisvaart JF et al: Intermediate to long-term follow-up indicates low risk of recurrence after double HIT endoscopic treatment for primary vesico-ureteral reflux. J Pediatr Urol 2012;8(4): 359–365.

Keren R et al: Risk factors for recurrent urinary tract infection and renal scarring. Pediatrics 2015;136(1):e12–e21.

Marchini GS et al: Robotic assisted laparoscopic ureteral reimplantation in children: Case matched comparative study with open surgical approach. J Urol 2011;185(5):1870–1875.

Martinell J et al: Pregnancies in women with and without renal scarring after urinary infections in childhood. BMJ 1990;300(6728):840–844.

Metcalfe CB et al: Reliability assessment of international grading system for vesicoureteral reflux. J Urol 2012;188:1490–1492.

Naseri M et al: Five cases of vesico-ureteric reflux in a family with an X-linked compatible trait. Pediatr Nephrol 2010;25(2):349–352.

Neel KF, Shillinger JF: The prevalence of persistent vesicoureteral reflux after 1 negative nuclear medicine cystogram. J Urol 2000; 164:1067–1069.

Oswald, J., Brenner, E., Schwentner, C., Deibl, M., Bartsch, G., Fritsch, H., & Radmayr, C. (2003). The intravesical ureter in children with vesicoureteral reflux: a morphological and immunohistochemical characterization. The Journal of urology, 170(6), 2423–2427.

Paquin AJ Jr: Ureterovesical anastomosis: The description and evaluation of a technique. J Urol 1959;82:573.

Peters C, Rushton HG: Vesicoureteral reflux associated renal damage: Congenital renal reflux nephropathy and acquired renal scarring. J Urol 2010;184(1):265–273.

Peters CA et al: Summary of the AUA guideline on management of primary vesicoureteral reflux in children. J Urol 2010;184(3):1134–1144.

Roberts KB et al: Urinary tract infection: Clinical practice guidelines for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2010;128(3): 595–610.

Routh JC et al: Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: Systematic review. Pediatrics 2010;125(5):1010–1019.

Salo J et al: Childhood urinary tract infections as a cause of chronic kidney disease. Pediatrics 2011;128(5):840–847.

Singh-Grewal D et al: Circumcision for the prevention of urinary tract infection in boys: A systematic review of randomised trials and observational studies. Arch Dis Child 2005;90(8):853–858.

Skoog SJ et al: Pediatric vesicoureteral reflux guidelines panel summary report: Clinical practice Guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. J Urol 2010;184(3):1145–1151.

Stephens FD: Treatment of megaloureters by multiple micturition. Austral NZ J Surg 1957;27:130.

Sung J, Skoog S: Surgical management of vesicoureteral reflux in children. Pediatr Nephrol 2012;27(4):551–561.

Tanagho EA, Pugh RCB: The anatomy and function of the ureterovesical junction. Br J Urol 1963;35:151.

Wang HH et al: Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: Systematic review and meta-analysis. J Urol 2015;193(3):963–969.

Yucel S, Baskin LS: Neuroanatomy of the ureterovesical junction: clinical implications. J Urol 2003;170(3):945–948.

Yucel S et al: Durability of a single successful endoscopic polytetrafluoroethylene injection for primary vesicoureteral reflux: 14 year followup results. J Urol 2007;178(1):265–268.

This page intentionally left blank

Bacterial Infections of the Genitourinary Tract

14

Mary K. Wang, MD; & Hillary L. Copp, MD, MS

Urinary tract infection (UTI) is a term that is applied to a variety of clinical conditions ranging from localized infection of the bladder with lower urinary tract symptoms to pyelonephritis with severe infection of the kidney and the potential for resultant urosepsis. UTI is one of the more common medical problems. It is estimated that UTIs lead to 8.2 million office visits and 1.7 million emergency room departments visits, resulting in at least $6 billion in healthcare expenditures (Stamm and Norrby, 2001; Litwin et al, 2005). UTIs are at times difficult to diagnose; some cases respond to a short course of a specific antibiotic, while others require a longer course of a broad-spectrum antibiotic. Accurate diagnosis and treatment of a UTI is essential to limit its associated morbidity and mortality and avoid prolonged or unnecessary use of antibiotics. Advances in our understanding of the pathogenesis of UTI and the development of new diagnostic tests have allowed physicians to appropriately tailor specific treatment for each patient. Unfortunately, because of the increasing rates of bacterial resistance to various antibiotics, medical therapies are becoming less efficacious (Kodner and Gupton, 2010).

EPIDEMIOLOGY

The epidemiology of UTI grouped by age and sex is shown in Table 14–1. In the neonatal period males are twice as likely as females to experience a UTI. From ages 1 to 6 months the rate of UTI is equal between genders, but from 6 to 12 months of age the rate of UTI in male and female children is 1 to 4. Overall, UTIs are more common in females (Shaikh et al, 2008; Hsiao et al, 2006). The incidence of UTI in uncircumcised males is 85% higher than circumcised males (Singh-Grewal et al, 2005). Risk factors for pediatric UTI include circumcision status, history of prior UTI, and sexual activity among older populations. In addition, anatomical abnormalities like vesicoureteral reflux, ureterocele, ureteropelvic junction obstruction, posterior urethral valves, neurogenic bladder, and bladder and bowel dysfunction portend a higher rate of UTI (Koff et al, 1998). At least 12–30% of patients with a history of symptomatic UTI will experience a recurrence (Conway et al, 2007). Upward of 60% of adult women will report having a UTI during their lifetime, and 11% will report having at least one infection per year (Fihn, 2003).

Approximately 7 million cases of acute cystitis are diagnosed yearly in young women (Schappert, 1999); this likely is an underestimate of the true incidence of UTI because at least 50% of all UTIs do not come to medical attention. The major risk factors for women 16–35 years of age are related to sexual intercourse, spermicide use, and diaphragm use. Certain medical conditions like diabetes, obesity, sickle cell trait, and anatomic congenital abnormalities can increase the risk of UTI (Hooton et al 1996). Later in life, the incidence of UTI increases significantly for both males and females. For women between 36 and 65 years of age, gynecologic surgery and bladder prolapse appear to be important risk factors. In men of the same age group, prostatic hypertrophy/obstruction, catheterization, and surgery are relevant risk factors. For patients older than 65 years, the incidence of UTI continues to increase in both sexes. Incontinence and chronic use of urinary catheters are important risk factors in these patients. In those younger than 1 year and those older than 65 years, the morbidity and mortality of UTI are the greatest (Shortliffe and McCue, 2002).

Data from the Urologic Diseases in North America Project suggested that the overall lifetime prevalence of UTI was 14,000 per 100,000 men (Griebling, 2005a) and 53,000 per 100,000 women (Griebling, 2005b). Overall medical expenditures for the treatment of UTIs in the United States were estimated to be $1 billion for men (Griebling, 2005a) and $2.5 billion for women (Griebling, 2005b). The increased cost in treatment of UTIs for women is due primarily to an increase in the trend toward using fluoroquinolones as a first-line therapy for UTI, despite recommendations of first-line empiric treatment with trimethoprim–sulfamethoxazole

Table 14–1. Epidemiology of UTI by age, group, and sex.

	Incidence (%)		
Age (y)	**Female**	**Male**	**Main risk factors**
<1	0.7	2.7	Foreskin, anatomic GU abnormalities
1–5	4.5	0.5	Anatomic GU abnormalities, functional GU abnormalities
6–15	4.5	0.5	Functional GU abnormalities
16–35	20	0.5	Sexual intercourse, diaphragm use
36–65	35	20	Surgery, prostate obstruction, catheterization
>65	40	35	Incontinence, catheterization, prostate obstruction

GU = genitourinary; UTI = urinary tract infection.

(Warren et al, 1999). However, the issue with TMP-SMX is increasing resistance. Bactrim use is not recommended in areas where baseline resistance is greater than 20% (Gupta et al, 2011). UTIs occurred in 2.4–2.8% of children. In this patient population, UTIs resulted in more than 1.1 million physician visits annually, accounting for 0.7% of the physician visits (Freedman, 2005).

PATHOGENESIS

Bacterial Entry

Understanding of the mode of bacterial entry, host susceptibility factors, and bacterial pathogenic factors is essential to tailoring appropriate treatment for the diverse clinical manifestations of UTI. There are four possible modes of bacterial entry into the genitourinary tract. It is generally accepted that periurethral bacteria with a uropathogen from the gut ascending into the urinary tract causes most UTI. The colonization of the urethra and migration to the bladder leads to invasion of the bladder mediated by pili and adhesions factors (Flores-Mireles et al, 2015). Most cases of pyelonephritis are caused by the ascent of bacteria from the bladder, through the ureter, and into the renal parenchyma. Consequently, the short nature of the female urethra combined with its close proximity to the vaginal vestibule and rectum likely predisposes women to more frequent UTIs than men (Nicolle et al, 1982).

Other modes of bacterial entry are uncommon causes of UTI. Hematogenous spread can occur in immunocompromised patients and in neonates. *Staphylococcus aureus*, *Candida* species, and *Mycobacterium tuberculosis* are common pathogens that travel through the blood to infect the urinary tract. Lymphatogenous spread through the rectal, colonic, and periuterine lymphatics has been postulated as a cause for UTI; however, currently, there is little scientific support to suggest that dissemination of bacteria through lymphatic channels plays a role in the pathogenesis of UTI. Direct extension of bacteria from adjacent organs into the urinary tract can occur in patients with intraperitoneal abscesses or vesicointestinal or vesicovaginal fistulas. Relapsing infection from an inadequately treated focus in the prostate or kidney may seed other parts of the urinary tracts.

Host Defenses

Host factors play an essential role in the pathogenesis of UTI. In females, normal vaginal and periurethral flora contain microorganisms like lactobacillus that help prevent uropathogenic colonization (Schaeffer, 2001). Unobstructed urinary flow with the subsequent washout of ascending bacteria is essential in preventing UTI. In addition, the urine itself has specific characteristics (its osmolality, urea concentration, organic acid concentration, and pH) that inhibit bacterial growth and colonization (Sobel, 1997; Schaeffer, 2001). It also contains factors that inhibit bacterial adherence, such as Tamm–Horsfall glycoprotein (THG) (Duncan, 1988; Pak et al, 2001; Wagenlehner et al, 2005). Is has been observed that the severity of the bacteriuria and the degree of inflammatory changes in the urinary tract were much greater in THG-deficit mice, suggesting that THG helps eliminate bacterial infection from the urinary tract and acts as a general host defense factor against UTI (Raffi et al, 2005). Urinary retention, stasis, or reflux of urine into the upper urinary tract can promote bacterial growth and subsequent infection. Consequently, any anatomic or functional abnormalities of the urinary tract that impede urinary flow can increase the host's susceptibility to UTI. These abnormalities include obstructive conditions at any level of the urinary tract, neurologic diseases affecting the function of the lower urinary tract, diabetes, and pregnancy. Similarly, the presence of foreign bodies (eg, stones, catheters, stents) allows the bacteria to hide from these host defenses.

The epithelium lining the urinary tract not only provides a physical barrier to infection but also has the capacity to recognize bacteria in order to activate innate host defenses. Neutrophils appear to be crucial in bacterial clearance from the kidney, but their role in the bladder is less defined (Haraoka et al, 1999). The urothelial cells express toll-like receptors (TLRs) that, on engagement by specific bacterial components, lead to production of inflammatory mediators (Chowdhury et al, 2004). Specific serum and urinary antibodies are produced by the kidney to enhance bacterial opsonization and phagocytosis and inhibit bacterial adherence. The protective role of both cellular and humoral immunity in preventing UTIs remains unclear; deficiency in B-cell or T-cell function has not been associated with the increased frequency of UTI or altered the course of the infection (Schaeffer, 2001; Svanborg et al, 1988). However, it should be noted that the same host defense mechanisms that help to prevent/

limit the infection (such as the inflammatory responses) can lead to cell and tissue damage. In the kidneys, cell damage and subsequent development of scarring may lead to pathological conditions such as hypertension, preeclampsia during pregnancy, and renal dysfunction and failure (Jahnukainen et al, 2005).

Cytotoxic cells also express mannose receptors that act on type 1 pili on many strains of *Escherichia coli*, and these receptors can facilitate phagocytosis. Some bacterial species of *E. coli* have adapted to this host defense and shed this type 1 pili (Hultgren et al, 1985). Many studies have demonstrated that there is selectivity in bacterial adherence to cells lining the urinary tract, and the degree of adherence correlates with colonization and infection. Women with recurrent UTIs have higher adherence of bacteria to their mucosal cells in vitro compared with women who never had an infection (Navas et al, 1994). The increased adherence may be due to having more binding sites for bacterial adhesins on their mucosal cells. Alternatively, these patients may not secrete soluble compounds, which normally compete for the same receptors that bind bacterial adhesins. Blood group antigens may constitute one group of these soluble compounds that inhibit bacterial adherence (Lomberg et al, 1986). These findings would suggest a genetic predisposition for UTI.

Other important host factors include the normal flora of the periurethral area or the prostate and the presence of vesicoureteral reflux. As mentioned previously, the normal female flora of the periurethral area composed of organisms such as lactobacillus provides a defense against the colonization of uropathogenic bacteria (Osset et al, 2001). Alterations in the periurethral environment (such as changes in the pH or estrogen levels or the use of antibiotics) can damage the periurethral flora, allowing uropathogens to colonize and subsequently to infect the urinary tract (Schaeffer et al, 1999). In men, the prostate secretes fluid containing zinc, which has potent antimicrobial activity (Fair et al, 1976). Finally, in children, the presence of vesicoureteral reflux does not increase their susceptibility to UTI but does allow bacteria to be inoculated into the upper tract and the infection to progress and lead to possible renal scarring.

Aging is associated with an increased susceptibility to UTI, in part because of the increased incidence of obstructive uropathy in men (Matsumoto, 2001; Nicolle, 2002) and alteration in the vaginal and periurethral flora from menopause in women (Foxman et al, 2001). Other causes include soiling of the perineum from fecal incontinence, neuromuscular diseases, increased instrumentation, and bladder catheterization (Ronald, 2002).

Bacterial Pathogenic Factors

Not all bacteria can adhere to and infect the urinary tract. Of the many strains of *Escherichia coli*, the uropathogens belong to a limited number of O, K, and H serogroups. They have increased adherence properties to uroepithelial cells (Blanco et al, 1996; Hovanec and Gorzynski, 1980; Orskov et al, 1982), resistance to the bactericidal activity of human serum (Bjorksten and Kaijser, 1978), production of hemolysin (Hughes et al, 1983; Koronakis and Hughes, 1996), and the increased expression of K capsular antigen (Whitfield and Roberts, 1999). The ability of *E. coli* to adhere to epithelial cells is mediated by ligands located on the tips of the bacterial fimbriae (pili). The ligands bind to glycolipids or glycoprotein receptors on the surface membrane of uroepithelial cells. The pili are classified by their ability to cause hemagglutination and the type of sugar that can block this process. P pili, which can agglutinate human blood, bind to glycolipid receptors on uroepithelial cells, erythrocytes (P blood group antigens), and renal tubular cells (Svenson et al, 1983). Type 1 pili, which can agglutinate guinea pig blood, bind to mannoside residues on uroepithelial cells (Ofek et al, 2000). P pili are observed in >90% of the *E. coli* strains causing pyelonephritis but <20% of the strains causing lower UTIs (Kallenius et al, 1981; Roberts et al, 1997a). In contrast, type 1 pili may help bacteria adhere to bladder mucosa (Connell et al, 1996; Martinez et al, 2000). Most uropathogenic *E. coli* have both types of pili. Once attachment to the uroepithelial cells occurs, other bacterial pathogenic factors become important. Most uropathogenic *E. coli* strains produce hemolysin, which initiates tissue invasion and makes iron available for the infecting pathogens (Hughes et al, 1983; Koronakis and Hughes, 1996). The presence of K antigen on the invading bacteria protects them from phagocytosis by neutrophils (Bortolussi et al, 1979; Evans et al, 1981). These factors allow the infecting pathogens to escape the various host defenses (Svanborg et al, 1996).

It has been observed that many bacteria such as *E. coli* can invade in the host cells, acting as opportunistic intracellular pathogens (Bower et al, 2005). Cytotoxic necrotizing factor, Afa/Dr adhesions, and type 1 pili have been shown to promote invasion into the host cells. Binding of FimH adhesin at the distal tip of type 1 pili to the host membrane leads to the recruitment of focal adhesin kinase, phosphoinositide-3-kinases, α-actinin, and vinculin, which results in localized actin rearrangements and engulfment of the bound bacterium by zippering of the membrane around the bacteria (reviewed by Anderson et al, 2004). The intracellular bacteria mature into biofilms, creating podlike bulges on the urothelial surface. The pods contain bacteria encased in a polysaccharide-rich matrix surrounded by a protective shell of uroplakin. The ability of the uropathogenic bacteria to transiently invade, survive, and multiply within the host cells and to create biofilms on genitourinary tract tissues may provide a mechanism for the persistence and recurrence of UTIs.

CAUSATIVE PATHOGENS

Most UTIs are caused by a single bacterial species. At least 80% of the uncomplicated cystitis and pyelonephritis in premenopausal women are due to *E. coli*, with most of pathogenic strains belonging to the O serogroups (Fihn, 2003). Other less common uropathogens include *Staphylococcus saprophyticus, Klebsiella, Proteus*, and *Enterobacter* spp. and enterococci. In hospital-acquired UTIs, a wider variety of causative organisms is found, including *Pseudomonas* and *Staphylococcus* spp. (Wagenlehner and Naber, 2000); UTIs caused by *S. aureus* often result from hematogenous dissemination. Group B β-hemolytic streptococci can cause UTIs in pregnant women (Wood and Dillon, 1981). *Staphylococcus saprophyticus*, once often regarded as urinary contaminants, can cause uncomplicated UTIs in young women. In children, the causative bacterial spectrum is slightly different but there is still a predominance of *E. coli* among inpatient and outpatient populations. *Enterobacter*, *Enterococcus*, and *Klebsiella* species make up the remainder of common culprits of pediatric UTI (Edlin et al, 2013; Saperston et al, 2014). Anaerobic bacteria, lactobacilli, corynebacteria, streptococci (not including enterococci), and *Staphylococcus epidermidis* are found in normal periurethral flora. They do not commonly cause UTIs in healthy individuals and are considered common urinary contaminants.

DIAGNOSIS

An uncomplicated UTI consists of an infection in an otherwise healthy patient with normal urinary tract anatomy. On the other hand, a complicated UTI can occur when anatomic abnormalities, immunocompromised state, or multi-drug-resistant bacteria allow for increased bacterial colonization or decreased therapeutic efficacy (Badalato and Kaufmann, 2016). Diagnosis of UTI in an adult is sometimes difficult to establish and relies on urinalysis and urine culture. Occasionally, localization studies may be required to identify the source of the infection. Most often, the urine is obtained from a voided specimen. Standard diagnosis of UTI is completed by urinalysis and urine culture of 100 CFU/mL (where CFU = colony-forming units) of bacteria.

American Academy of Pediatrics (AAP) guidelines suggest that if a urinalysis demonstrates positive leukocyte esterase or nitrite on testing, urine should be obtained via catheterization or suprapubic aspiration for culture prior to start antimicrobial therapy (Roberts, 2011). In children who are not toilet-trained, a urine collection device, such as a bag, is placed over the genitalia, and the urine is cultured from the bagged specimen. These two methods of urine collection are easy to obtain, but potential contamination from the vagina and perirectal area may occur. The National Institute for Health and Care Excellence (NICE) and American Association of Pediatrics (AAP) guidelines recommend urine testing be performed prior to treatment for UTI; however, despite this recommendation, >40% of children with antibiotic-treated UTI do not receive recommended urine testing (Copp et al, 2013). A negative urine culture via a bagged specimen in children ensures that there is a low likelihood of infection and an alternate source of symptoms should be pursued. A positive urine culture via a bagged specimen may represent contamination or true infection, and a catheterized specimen should be obtained (Roberts, 2011). Suprapubic aspiration avoids potential contamination; however, because of its invasiveness, it is rarely used except in selected patients. Urine obtained from a urinary catheter is less invasive than a suprapubic aspiration and is less likely to be contaminated than that obtained from a voided specimen. If a patient has an indwelling catheter, a urine specimen should be obtained from the collection port on the catheter.

Urinalysis

The urine can be immediately evaluated for leukocyte esterase, a compound produced by the breakdown of white blood cells (WBCs) in the urine and is 95% sensitive for UTI in children with symptoms. Positive leukocyte esterase indicates the presence of 5–15 WBC per high-power field (hpf). Urinary nitrite is produced by reduction of dietary nitrates by many Gram-negative bacteria. Esterase and nitrite can be detected by a urine dipstick and are more reliable when the bacterial count is >100,000 colony-forming units (CFUs) per milliliter. Combined positive nitrite and leukocyte esterase on urine dipstick analysis is 80–90% sensitive and 60–98% specific for UTI (Shaikh et al, 2007). When bacteria counts are >100,000 CFU/mL, bacteria can be detected microscopically (Jenkins et al, 1986). The sensitivity and specificity of these tests are shown in Table 14–2 (Williams et al, 2010). A combination of these tests may help to identify those patients in whom urine culture will be positive. Conversely, when esterase, nitrite, blood, and protein are absent in a urine sample, <2% of the urine samples will be positive by culture, providing a >98% negative predictive value and a sensitivity of 98% (Patel et al, 2005). Microscopic examination of the urine for WBCs and bacteria is performed after centrifugation. For children, urine concentration should be taken into consideration when diagnosing infants with UTI. A pyuria threshold of 3 WBC/hpf in dilute urine and 6 WBC/hpf in concentrated urine is noted for a diagnosis of UTI in infants (Chaudhari et al,

Table 14–2. Sensitivity and specificity of urinalysis.

Tests	Sensitivity (%)	Specificity (%)
Esterase (E)	79 (73–84)	87 (80–92)
Nitrite (N)	49 (41–57)	98 (96–99)
E + N	45 (30–61)	98 (96–99)
WBC	74 (67–80)	86 (82–90)
Bacteria	88 (75–94)	92 (83–96)

WBC = white blood cell.

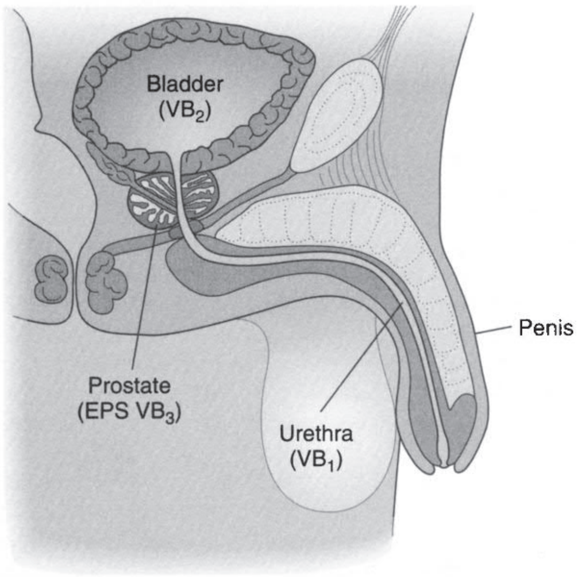
2016). A recent systematic review of the literature indicates that urinalysis is more effective in the diagnosis of UTI as determined by urine culture in children older than 2 years than for younger children (Mori et al, 2010).

Urine Culture

The gold standard for identification of UTI is the quantitative culture of urine for specific bacteria. The urine should be collected in a sterile container and cultured immediately after collection. When this is not possible, the urine can be stored in the refrigerator for up to 24 hours. The sample is then diluted and spread on culture plates. Each bacterium will form a single colony on the plates. It can take up to 3–4 days to receive results with the antibiotic sensitivities. The number of colonies is counted and adjusted per milliliter of urine (CFU/mL). Defining the CFU/mL that represents clinically significant infection can be difficult. It is dependent on the method of collection, the sex of the patient, and the type of bacteria isolated (Table 14–3). Traditionally, cultures demonstrating 100,000 CFU/mL are considered diagnostic of a UTI, but now AAP guidelines suggest pyuria and 50,000 CFU/mL of a single organism are diagnostic of UTI (Roberts, 2011).

Localization Studies

Occasionally, it is necessary to localize the site of infection. For upper urinary tract localization (Lorentz, 1979), the bladder is irrigated with sterile water and a ureteral catheter is placed into each ureter. A specimen is collected from the renal pelvis. Culture of this specimen will indicate whether infection in the upper urinary tract is present. In men, infection in the lower urinary tract can be differentiated (Figure 14–1) (Meares and Stamey, 1968). A specimen is collected at the beginning of the void and represents possible infection in the urethra. Next, a midstream specimen is collected and represents possible infection in the bladder. The prostate is then massaged and the patient is asked to void again. This specimen represents possible infection of the prostate.



▲ Figure 14–1. Localization of lower urinary tract infection. A positive culture in the voided bladder urine specimen VB_1 suggests infection of the urethra, while in VB_2, an infection of the bladder, and in EPS or VB_3, an infection of the prostate.

Table 14–3. Probability of UTIs based on urine culture.

Collection	CFU	Probability of infection (%)
Suprapubic	Gram-negative any Gram positive >1000	>99
Catheterization	$>10^5$ 10^{4-5} 10^{3-4} $<10^3$	95 Likely Repeat Unlikely
Clean catch		
Male	$>10^4$	Likely
Female	3 specimens: $>10^5$ 2 specimens: $>10^5$ 1 specimen: $>10^5$ 5×10^4–10^5 1–5 × 10^4 symptomatic 1–5 × 10^4 nonsymptomatic $<10^4$	95 90 80 Repeat Repeat Unlikely Unlikely

CFU = colony-forming unit; UTI = urinary tract infection.

ANTIBIOTICS

Treatment with antimicrobial agents has minimized the morbidity and mortality associated with UTIs. The goal in treatment is to eradicate the infection by selecting the appropriate antibiotics that would target specific bacterial susceptibility. The general principles for selecting the appropriate antibiotics include consideration of the infecting pathogen (antibiotic susceptibility, single-organism vs polyorganism infection, pathogen vs normal flora, community vs hospital-acquired infection); the patient (allergies, underlying diseases, age, previous antibiotic therapy, other medications currently taken, outpatient vs inpatient status, pregnancy); and the site of infection (kidney vs bladder vs prostate). By utilizing the antibiogram available through >95% of hospitals

Table 14–4. Antibiotics that require dosage adjustments for liver and renal diseases.

- Renal diseases (Cr clearance <30 mL/min)
  - Aminoglycosides
  - β-Lactams
    - Cefoxitin, ceftizoxime
    - Cefonicid, ceftazidime
    - Cefuroxime, cefepime
    - Cefpirome, moxalactam
  - Carbenicillin, ticarcillin, ticarcillin–clavulanate
  - Vancomycin
  - Tetracyclines (except doxycycline)
  - Sulfonamides
- Hepatic diseases (with elevated bilirubin)
  - Chloramphenicol
  - Tetracyclines
  - Clindamycin, rifampin, pefloxacin
- Renal–hepatic diseases
  - Ceftriaxone
  - Cefoperazone
  - Carbenicillin
  - Ticarcillin
  - Azlocillin
  - Mezlocillin
  - Piperacillin

Table 14–5. Recommended antimicrobial agents for common genitourinary pathogens.

Bacteria	Oral therapy	Parenteral therapy
Gram-positive cocci		
Staphylococcus aureus	Nafcillin, nitrofurantoin, ciprofloxacin	Nafcillin, vancomycin
Staphylococcus epidermidis	Ampicillin, nitrofurantoin, ciprofloxacin	Ampicillin, penicillin G
Staphylococcus saprophyticus	Ampicillin, nitrofurantoin, ciprofloxacin	Ampicillin, penicillin G
Streptococcus, group D		
S. faecalis (enterococci)	Ampicillin, nitrofurantoin	Ampicillin plus gentamicin
S. bovis	Penicillin G, ampicillin	Ampicillin, vancomycin
Streptococcus, group B	Ampicillin, cephalosporin	Ampicillin, cephalosporin
Gram-negative cocci		
Neisseria gonorrhoeae	Ciprofloxacin plus doxycycline	Ceftriaxone
Gram-negative rods		
Escherichia coli	TMP-SMX, ciprofloxacin, nitrofurantoin*	Gentamicin
Enterobacter spp.	TMP-SMX, ciprofloxacin, nitrofurantoin*	Gentamicin plus piperacillin
Gardnerella vaginalis	Metronidazole, ampicillin	Metronidazole
Klebsiella spp.	TMP-SMX, ciprofloxacin	Gentamicin plus cephalosporin
Proteus spp.	Ampicillin, TMP-SMX, ciprofloxacin	Ampicillin, gentamicin
Pseudomonas aeruginosa	Carbenicillin, tetracycline, ciprofloxacin	Gentamicin plus piperacillin
Serratia spp.	TMP-SMX, carbenicillin	TMP-SMX, amikacin
Other pathogens		
Chlamydiae	Tetracycline, erythromycin	Tetracycline, erythromycin
Mycoplasmas, ureaplasmas	Tetracycline, erythromycin	Tetracycline, erythromycin
Obligate anaerobes	Metronidazole, clindamycin	Metronidazole, clindamycin

TMP-SMX = trimethoprim plus sulfamethoxazole.

[a]Nitrofurantoin should not be administered when treating febrile UTI/pyelonephritis.

and communities, susceptibility patterns can help guide empiric treatment (Ernst et al, 2004). Because most antibiotics are cleared from the body by the liver or the kidney, certain antimicrobial agents need to be adjusted in the presence of liver or renal disease (Table 14–4). Table 14–5 lists the common uropathogens and the recommended oral and intravenous antimicrobial agents for treatment. Tables 14–6 and 14–7 list the common sites of UTI, the recommended treatment, and the duration of therapy for adults and pediatric patients. In patients with recurrent UTIs or those who are at risk for UTI (such as children with vesicoureteral reflux), prophylactic antibiotics may be used. Table 14–8 lists common prophylactic regimens. In addition, minimum inhibitory concentration (MIC) demonstrates the lowest amount of antibiotic necessary to exhibit antimicrobial activity against a certain pathogen. While it would seem straightforward to pick the antibiotic with the lowest MIC reported for antibiotic sensitivities, the pharmacokinetics of the drug must be considered. There must be a drug concentration above the MIC to achieve adequate concentration at site of infection (McKinnon and Davis, 2004).

Trimethoprim–Sulfamethoxazole

Trimethoprim–sulfamethoxazole (TMP-SMX) is commonly used to treat many UTIs, except those caused by *Enterococcus* and *Pseudomonas* spp. It interferes with the bacterial metabolism of folate. TMP-SMX is highly effective and relatively

Table 14–6. Recommended antimicrobial agents and duration of therapy based upon the type of UTI for adults.

Diagnosis	Choice of antibiotics	Duration of therapy
Cystitis	1st: TMP-SMX 2nd: Fluoroquinolone	1–3 days
Pyelonephritis	1st: Gluoroquinolone 2nd: 2nd-generation cephalosporin 3rd: Aminopenicillin/BLI	7–10 days
Complicated UTI[a]	1st: Fluoroquinolone 2nd: Aminopenicillin/BLI 3rd: 3rd-generation cephalosporin Aminoglycosides	Afebrile: 2 weeks Febrile: continue for additional 3–5 days after last fever (minimum 2 weeks)
Prostatitis	1st: Fluoroquinolone 2nd: 2nd-generation cephalosporin 3rd: 3rd-generation cephalosporin	Acute: 2 weeks Chronic: 4–6 weeks
Epididymitis	1st: Fluoroquinolone 2nd: 2nd-generation cephalosporin *or* 1st: Doxycycline 2nd: Macrolide	14 days
Urethritis[b]	1st: IM ceftriaxone + azithromycin 2nd: Doxycycline	Single dose 7 days

[a] Complicated UTI: infection in the setting of metabolic, immunocompromised, functional, or anatomic abnormality

[b] If suspicion of sexual transmitted disease as source.

Table 14–7. Recommended antimicrobial agents and duration of therapy based on the type of UTI for children.

Diagnosis	Choice of antibiotics	Dose	Duration of therapy
Cystitis	1st: Cephalexin	50–100 mg/kg in 4 doses	7 days
	2nd: Nitrofurantoin	5 mg/kg in 2 doses	
	3rd: TMP-SMX	8–10 mg/kg of TMP in 2 doses	
Pyelonephritis	1st: Amoxicillin–clavulanic acid, 1st-line cephalosporin	20–40 mg/kg in 3 doses	7–14 days
	2nd: 3rd- or 4th-generation cephalosporin (Ceftriaxone)	75 mg/kg in 1 dose	

Table 14–8. Prophylactic antibiotics regimen for children and adults.

Adult	Children
Cephalexin 250 mg daily	TMP-SMX 2 mg/kg daily
Ciprofloxacin 250 mg daily	Nitrofurantoin 1–2 mg/kg daily
Trimethoprim 100 mg daily	Cephalexin[a] 10 mg/kg daily
Nitrofurantoin 50 or 100 mg daily	Amoxicillin[a] 10 mg/kg daily
Nitrofurantoin macrocrystals 100 mg daily	Ampicillin[a] 20 mg/kg daily
TMP-SMX 40/200 mg daily	

[a] Can be given in newborns <2 months of age.

inexpensive. Adverse reactions occur in 6–8% of patients using this medication; they include hypersensitivity reactions, rashes, gastrointestinal upset, leukopenia, thrombocytopenia, and photosensitivity. TMP-SMX should not be used in patients who have a folic acid deficiency state, glucose-6-phosphate dehydrogenase deficiency, or acquired immunodeficiency syndrome (AIDS), or in pregnant patients. It is the most frequently prescribed antibiotic for uncomplicated UTI (Huang and Stafford, 2002) and is the recommended first-line treatment, unless there is a greater than 20% baseline resistance rate. TMX can be used as monotherapy in the treatment of uncomplicated UTI without significant loss in antibacterial coverage (Nguyen et al, 2010).

▶ Fluoroquinolones

Fluoroquinolones have a broad spectrum of activity, especially against Gram-negative bacteria. Although they have adequate activity against *Staphylococci* species, fluoroquinolones do not have good activity against *Streptococci* species and anaerobic bacteria. They interfere with the bacterial DNA gyrase, preventing bacterial replication. Although they are highly effective in the treatment of UTI, fluoroquinolones are relatively expensive. Adverse reactions are infrequent and include mild gastrointestinal effects, dizziness, and lightheadedness. Fluoroquinolones should not be used in patients who are pregnant and should be used judiciously in children because of potential damage to developing cartilage. Because of their broad spectrum of activity, fluoroquinolones have gained popularity in the empiric treatment of both uncomplicated and complicated UTIs (Schaeffer, 2002). The Infectious Disease Society of America recommends that fluoroquinolones be utilized as second-line therapy or for a complicated UTI.

▶ Nitrofurantoin

Nitrofurantoin has good activity against most Gram-negative bacteria (except for *Pseudomonas* and *Proteus* spp.), *Staphylococci*, and *Enterococci* species. It inhibits bacterial enzymes and DNA activity. Nitrofurantoin is highly effective in the treatment of UTI and is relatively inexpensive. It should not be used in patients with renal impairment as the drug may not reach adequate concentrations in the urine and, thus, it is not recommended in patients with a creatinine clearance below 30 mL/min. Adverse reactions are relatively common and include gastrointestinal upset, peripheral polyneuropathy, and hepatotoxicity. Long-term use may result in pulmonary hypersensitivity reaction and interstitial changes. In addition, it should be used with caution in elderly patients. Nitrofurantoin becomes highly concentrated in the urine but demonstrates poor tissue penetration. For this reason, it should not be used for complicated UTI, pyelonephritis, or prostatitis. With increasing awareness of this antibiotic and its activity against common uropathogens, nitrofurantoin usage in the treatment of uncomplicated UTIs has increased (Huang and Stafford, 2002).

Aminoglycosides

Aminoglycosides are commonly used in the treatment of complicated UTI. They are highly effective against most Gram-negative bacteria. When combined with ampicillin, they are effective against enterococci. They inhibit bacterial DNA and RNA synthesis. The principal adverse effects of aminoglycosides are nephrotoxicity and ototoxicity. Aminoglycosides are used primarily in patients with complicated UTIs who require intravenous antibiotics (Santucci and Krieger, 2000). Aminoglycosides, like tobramycin, can be given as a single daily dosing; this regimen is directed toward obtaining higher peak and lower trough levels in order to achieve more effective microbial killing while reducing toxicity (Carapetis et al, 2001).

Cephalosporins

Cephalosporins have good activity against most uropathogens (Garcia-Rodriguez and Munoz Bellido, 2000). First-generation cephalosporins have good activity against Gram-positive bacteria, *E. coli*, and *Proteus* and *Klebsiella* spp. Second-generation cephalosporins have increased activity against anaerobes and *Haemophilus influenzae.* Third- and fourth-generation cephalosporins have broader coverage against Gram-negative bacteria but less against Gram-positive bacteria. The cephalosporins inhibit bacterial cell wall synthesis. Adverse reactions include hypersensitivity and gastrointestinal upset. Keflex is a common first-line empiric agent in children based on sensitivity profiles for most uropathogens and has the added benefit that it can be utilized in children less than 2 months of age. Oral cephalosporins have been used effectively in the empiric treatment of uncomplicated UTIs (Lawrenson and Logie, 2001); in children with febrile UTI/pyelonephritis, oral third-generation cephalosporins such as cefixime have been shown to be safe and effective (Hoberman et al, 1999).

Penicillins

First-generation penicillins are ineffective against most uropathogens and are not commonly used in the treatment of UTI. However, the aminopenicillins (amoxicillin and ampicillin) have good activity against *Enterococci*, *Staphylococc*i, *E. coli*, and *Proteus mirabilis.* However, Gram-negative bacteria can quickly develop resistance to many aminopenicillins. The addition of β-lactamase inhibitors such as clavulanic acid renders the aminopenicillins more active against the Gram-negative bacteria. Although penicillins and aminopenicillins are inexpensive, the addition of the β-lactamase inhibitors makes them more expensive. Adverse reactions include hypersensitivity (which can be immediate or delayed), gastrointestinal upset, and diarrhea. In general, penicillins are rarely used in the treatment of UTI unless they are combined with β-lactamase inhibitors (Sotto et al, 2001) except in the pediatric population, where they are frequently utilized for antibiotic prophylaxis and UTI treatment in neonates.

Antibiotic Resistance

The use of antibiotics has significant consequences for the treatment of future infection. Drug resistance among uropathogens has increased steadily during the past several years (Miller and Tang, 2004) and has much geographic variability. The use of broad-spectrum antibiotics has long been associated with the development of methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile,* and vancomycin-resistant enterococci (VRE) superinfection (Pallet and Hand, 2010). It is recognized that antibiotic use selects for and maintains antibiotic resistance as well as enhances its spread. Individuals prescribed an antibiotic in the primary care setting for a urinary infection develop bacterial resistance to that antibiotic (reviewed by Costelloe et al, 2010). The effect appears to be the greatest in the first month following treatment but may persist up to 12 months. Local hospital antibiograms, which quantifies drug resistance seen at the hospital microbiology laboratory during a particular year, can provide information regarding local antibiotic resistance among bacteria for a specific locale. Evaluating these antibiograms together, some important trends in drug resistance can be seen (Kahlmeter, 2003). Among uropathogens, particularly *E. coli*, resistance to ampicillin (45%), trimethoprim–sulfamethoxazole (24%), and cefazolin (4%) were high. Resistance to nitrofurantoin and fluoroquinolones were generally lower (<3%). However, with more extensive usage, resistance to these drugs is increasing (Johnson et al, 2008; Karaca et al, 2005). Even aminoglycosides that are regarded as an effective, first-line choice for the treatment of complicated UTIs are not immune to the development of resistance as demonstrated by resistance rates of 2–10% (Lau et al, 2004; The Surveillance Network). To limit the development of antibiotic resistance among uropathogens, judicial usage of antibiotics (duration and selection of the antibiotics) will be required. An uncomplicated first-time cystitis does not require a 13-day course of treatment with a fluoroquinolone but simply a 3-day course of treatment with TMP-SMX. For the second time in the United States, a new "superbug" *E. coli* has been found. This bacterial variant has shown resistance to the last-resort antibiotic of colistin. There is concern that this genetic resistance pattern that demonstrated resistance to colistin could transfer its gene to other *E. coli* bacteria, thereby potentially perpetuating a completely antibiotic-resistant strain of bacterium (Anonymous, 2016).

Probiotics

The intestinal microbial flora consists of diverse bacterial species that inhabit the gastrointestinal tract. These bacteria are integral to the ontogeny and regulation of the immune system and protection of the body from infection. The interaction of the gut microbial flora with intestinal epithelial cells and immune cells exerts beneficial effects on the urinary tract. Intermittent and chronic antibiotic usage damages the intestinal flora. Probiotics such as lactic acid bacteria and bifidobacteria can restore normal intestinal flora and promote good host defense (Abad and Safdar, 2009). However, they should be avoided in critically ill and immunocompromised patients because of the risk of sepsis. Probiotics are commonly consumed as part of fermented foods with specially added active live cultures, such as in dairy yogurt or soy yogurt, or as dietary supplements. A recent Cochrane literature review evaluated nine different studies and found no benefit of probiotics versus placebo (Schwenger et al, 2015). Cranberry supplements have also been studied, and drinking 5 mL/kg per day was shown to reduce the number of overall recurrent infections, but did not significantly decrease the amount of children having at least one recurrent UTI (Salo et al, 2012). Several adult studies have been performed, and there is conflicting evidence for cranberry use efficacy and UTI prevention.

CLINICAL PRESENTATION OF KIDNEY INFECTION

Acute Pyelonephritis

Acute pyelonephritis is defined as inflammation of the kidney and renal pelvis, and its diagnosis is usually made clinically.

A. Presentation and Findings

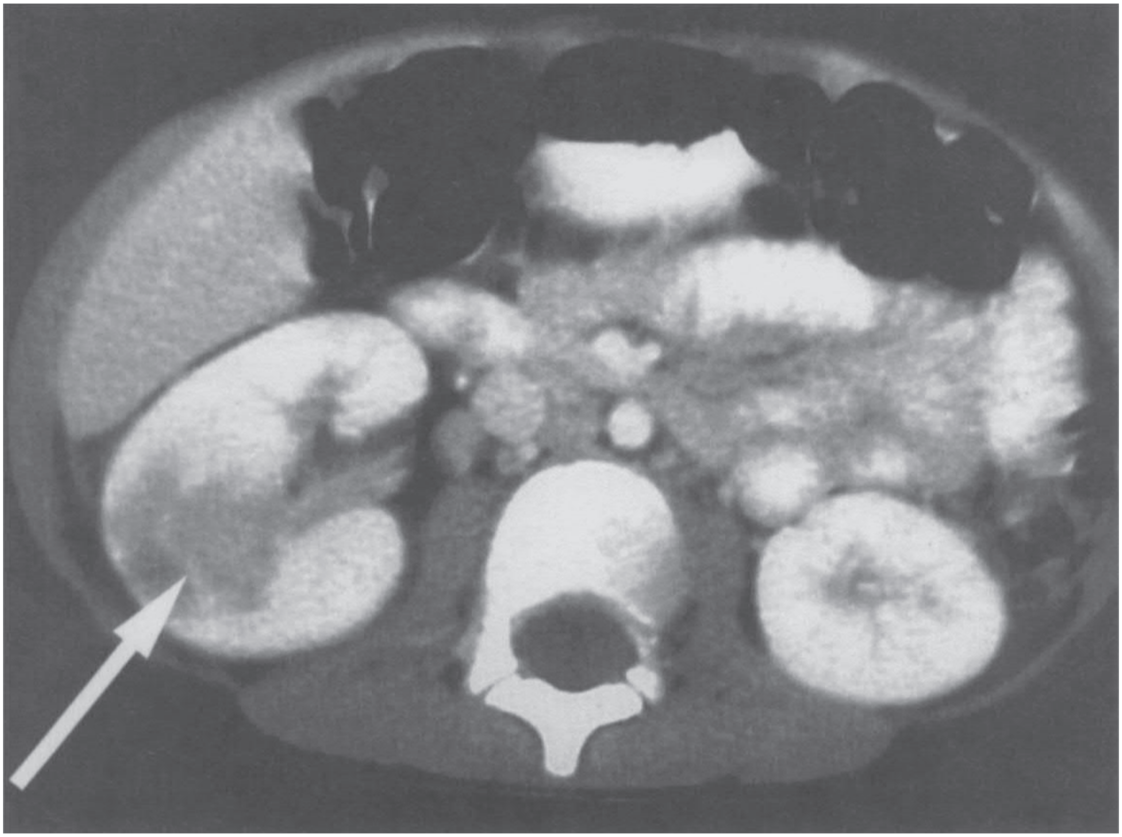
Patients with acute pyelonephritis present with chills, fever, and costovertebral angle tenderness. They often have accompanying lower tract symptoms such as dysuria, frequency, and urgency. Sepsis may occur, with 20–30% of all systemic sepsis resulting from a urine infection. Urinalysis commonly demonstrates the presence of WBCs and red blood cells in the urine. Leukocytosis, increased erythrocyte sedimentation, and elevated levels of C-reactive protein are commonly seen on blood analysis. Bacteria are cultured from the urine when the culture is obtained before antibiotic treatment is instituted. *E. coli* is the most common causative organism, accounting for 70–80% of the cases. *Klebsiella, Proteus, Enterobacter, Pseudomonas, Serratia,* and *Citrobacter* spp. account for the remaining cases. Of the Gram-positive bacteria, *Streptococcus faecalis* and *S. aureus* can be important causes of pyelonephritis. In reproductive-age women, sexual activity and patient and family history of UTI are associated with an increased risk of developing pyelonephritis. Diabetes and urinary incontinence also independently increase this risk (Scholes et al, 2005).

B. Radiographic Imaging

Although seldom required, contrast-enhanced computed tomography (CT) scans can accurately demonstrate findings, confirming the diagnosis of pyelonephritis (Dacher et al, 1993). Acute bacterial infection causes constriction of peripheral arterioles and reduces perfusion of the affected renal segments. Perfusion defects, which can be segmental, multifocal, or diffuse, are areas of reduced signal density (Figure 14–2). Renal enlargement, attenuated parenchyma, and a compressed collecting system are other characteristic findings on CT scan. However, CT scan is not necessary unless the diagnosis is unclear or the patient is not responding after 48–72 hours of culture specific antibiotic therapy. Renal ultrasonography is an ideal imaging modality in the pediatric population, and CT scanning should be reserved for select children secondary to radiation exposure risks. Radionuclide study with ^{99m}Tc-dimercaptosuccinic acid is equally sensitive in detecting the perfusion defects of pyelonephritis, but this is rarely performed in the acute stage (Levtchenko et al, 2001). In patients with acute pyelonephritis, renal ultrasonography is important to rule out concurrent urinary tract obstruction but cannot reliably detect inflammation or infection of the kidney.

C. Management

The management of acute pyelonephritis depends on the severity of the infection (Ghiro et al, 2002; Nickel, 2001). In patients who have toxicity due to associated septicemia, hospitalization is warranted. Approximately 10–30% of all adult patients with acute pyelonephritis require hospitalization, with an incidence of 15–17 per 10,000 for women and 3–4 per 10,000 for men. The cost of treating acute pyelonephritis has been estimated at over $2 billion per year (Czaja et al, 2007). The usual pathogen is *E. coli* or other *Enterobacter* sp. for which empiric therapy with intravenous ampicillin and aminoglycosides is effective against a broad range of uropathogens, including enterococci and *Pseudomonas* species. Alternatively, amoxicillin with clavulanic acid or a third-generation cephalosporin can be used. For adults, treatment with fluoroquinolones or TMP-SMX is well tolerated and effective. Outpatient treatment with an initial parental antibiotic (ceftriaxone or gentamicin) followed by oral therapy for 7–14 days has been shown to have a 12% admission rate (Czaja et al, 2007). On the other hand, any



▲ **Figure 14–2.** Acute pyelonephritis. Computed tomography scan with intravenous contrast demonstrates a perfusion defect (*white arrow*) and enlargement of the affected kidney.

pregnant patient with concerns for pyelonephritis requires admission with parental antibiotics secondary to the risk of preterm labor. Some patients in whom acute pyelonephritis develops will require follow-up radiologic examination such as voiding cystourethrogram or cystoscopy.

Treatment for children can be usually be performed in an outpatient setting unless there is inability to tolerate an oral antibiotic. In a study of community-acquired UTIs in children hospitalized in a tertiary center (Marcus et al, 2005), it was noted that 40% of the culture-proven UTIs were caused by non–*E. coli* pathogens. Non–*E. coli* infections were more commonly found in males who had renal abnormalities and who had received antibiotic therapy in the prior month. Non–*E. coli* uropathogens were often resistant to cephalosporins and aminoglycosides. Fever from acute pyelonephritis may persist for several days despite appropriate therapy. If bacteremia is present, parenteral therapy should be administered for 7–10 days and then the patient should be switched to oral treatment for an additional10–14 days.

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a necrotizing infection characterized by the presence of gas within the renal parenchyma or perinephric tissue. About 95% of patients with emphysematous pyelonephritis have diabetes; women experience this condition 6 times more commonly than men. Other contributing factors include renal failure, immunosuppression, obstructed upper tracts, and polycystic kidneys (Olvera-Posada et al, 2012).

A. Presentation and Findings

Patients with emphysematous pyelonephritis present with fever, flank pain, and vomiting that fails initial management with parenteral antibiotics (Tang et al, 2001). Pneumaturia may be present. Bacteria most frequently cultured from the urine include *E. coli* (66%)*; Klebsiella pneumonia* (26%)*;* and *Proteus, Pseudomonas*, *and Streptococcus* spp.

B. Radiographic Imaging

The diagnosis of emphysematous pyelonephritis is made after radiographic examination. Gas overlying the affected kidney may be seen on a plain abdominal radiograph (kidneys, ureters, bladder [KUB]). CT scan is much more sensitive in detecting the presence of gas in the renal parenchyma than renal ultrasonography.

C. Management

In the management of emphysematous pyelonephritis, prompt control of blood glucose and relief of urinary obstruction are essential, in addition to fluid resuscitation and parenteral antibiotics. The mortality rate is 19–40% (Huang and Tseng, 2000; Wan et al, 1998). Poor prognostic factors include high serum creatinine level (>1.4), low platelet count (<60,000 μL^{-1}), and the presence of renal/perirenal fluid in association with a bubbly/loculated gas pattern or gas in the collecting system (Wan et al, 1998). In combination with medical treatment, percutaneous drainage appears to be helpful in accelerating resolution of the infection and minimizing the morbidity and mortality of the infection, with up to 66% success rates reported (Chen et al, 1997; Huang and Tseng, 2000). In the presence of two or more of the above risk factors, nephrectomy is recommended if there is no function in the affected kidney. About 3–4 weeks of parenteral antibiotic therapy is usually required.

▶ Chronic Pyelonephritis

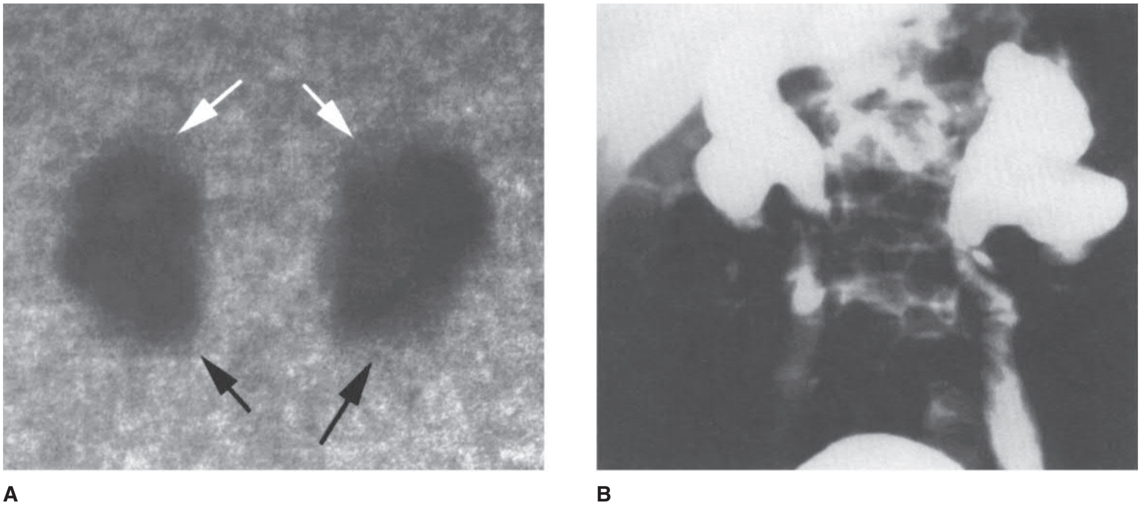
Chronic pyelonephritis results from repeated renal infection, which leads to scarring, atrophy of the kidney, and subsequent renal insufficiency. The diagnosis is made by radiologic or pathologic examination rather than from clinical presentation.

A. Presentation and Findings

Many individuals with chronic pyelonephritis have no symptoms, but they may have a history of frequent UTIs. In children, there is a strong correlation between renal scarring and recurrent UTIs (Wennerstrom et al, 2000). The developing kidney appears to be very susceptible to damage, and this susceptibility appears to be age-dependent, with scarring development reported in a range from 10% to 80% of children after an episode of acute pyelonephritis (Chiou et al, 2001; Hoberman et al, 2003). Renal scarring induced by UTIs is rarely seen in adult kidneys. Because patients with chronic pyelonephritis are often asymptomatic, the diagnosis is made incidentally when radiologic investigation is initiated to evaluate for the complications associated with renal insufficiency, such as hypertension, visual impairments, headaches, fatigue, and polyuria. In these patients, urinalysis may show leukocytes or proteinuria but is likely to be normal. Serum creatinine levels reflect the severity of the renal impairment. Urine cultures are positive only when there is an active infection.

B. Radiographic Imaging

Intravenous pyelogram or CT scan can readily demonstrate a small and atrophic kidney on the affected side. Focal, coarse renal scarring with clubbing of the underlying calyx is characteristic. Ultrasonography similarly can demonstrate these findings. Di(mercaptosuccinic acid) (DMSA) is the best imaging modality to look for renal scarring (Figure 14–3) (Stoller and



▲ **Figure 14–3.** Chronic pyelonephritis. Multiple parenchymal defects (*white and black arrows*) are seen on DMSA scan *(**A**)*, suggestive of scarring from recurrent infection. Voiding cystourethrogram *(**B**)* revealed high-grade reflux in this patient.

Kogan, 1986), with up to 100% sensitivity and 87% specificity for detecting scars from pyelonephritis (Chiou et al, 2001). Areas of scarring are seen as photopenic areas.

C. Management

The management of chronic pyelonephritis is somewhat limited because renal damage incurred by chronic pyelonephritis is not reversible. Eliminating recurrent UTIs and identifying and correcting any underlying anatomic or functional urinary problems such as obstruction or urolithiasis can prevent further renal damage. In children, evaluation for vesicoureteral reflux with a voiding cystourethrogram is important to eliminate a risk factor for recurrent pyelonephritis and renal scarring. Long-term use of continuous prophylactic antibiotic therapy may be required to limit recurrent UTIs and renal scarring. Rarely, removal of the affected kidney may be necessary due to hypertension or having a large stone burden in a nonfunctioning kidney.

Renal Abscesses

Renal abscesses result from a severe infection that leads to liquefaction of renal tissue; this area is subsequently sequestered, forming an abscess. They can rupture out into the perinephric space, forming **perinephric abscesses**. When the abscesses extend beyond the Gerota's fascia, **paranephric abscesses** develop. Historically, most renal/perinephric abscesses result from hematogenous spread of staphylococci, particularly from infected skin lesions. Patients with diabetes, those undergoing hemodialysis, or intravenous drug abusers have been at high risk for developing renal abscesses. With the development of effective antibiotics and better management of diseases such as diabetes and renal failure, renal/perinephric abscesses due to Gram-positive bacteria are less prevalent, with a predominance of abscesses caused by *E. coli* (75%), with the remaining 25% caused by *Klebsiella, Proteus, Enterobacter, Streptococcus*, and *S. aureus*. Abscesses that form in the renal cortex are likely to arise from hematogenous spread, whereas those in the corticomedullary junction are caused by Gram-negative bacteria in conjunction with some other underlying urinary tract abnormalities, such as stones or obstruction.

A. Presentation and Findings

The most common presenting symptoms in patients with renal/perinephric abscesses include fever, flank or abdominal pain, chills, and dysuria. Many of the symptoms have lasted for more than 2 weeks. Risk factors include nephrolithiasis, genitourinary instrumentation, vesicoureteral reflux and diabetes mellitus (>50%) (Velciov et al, 2011). A flank mass may be palpated in some patients. Urinalysis usually demonstrates WBCs; however, it may be normal in approximately 25% of the cases, especially if there the collecting system is obstructed (Thorley et al, 1974). Urine cultures identify a causative organism in 75%, and blood cultures are positive in more than 50% of patients.

B. Radiographic Imaging

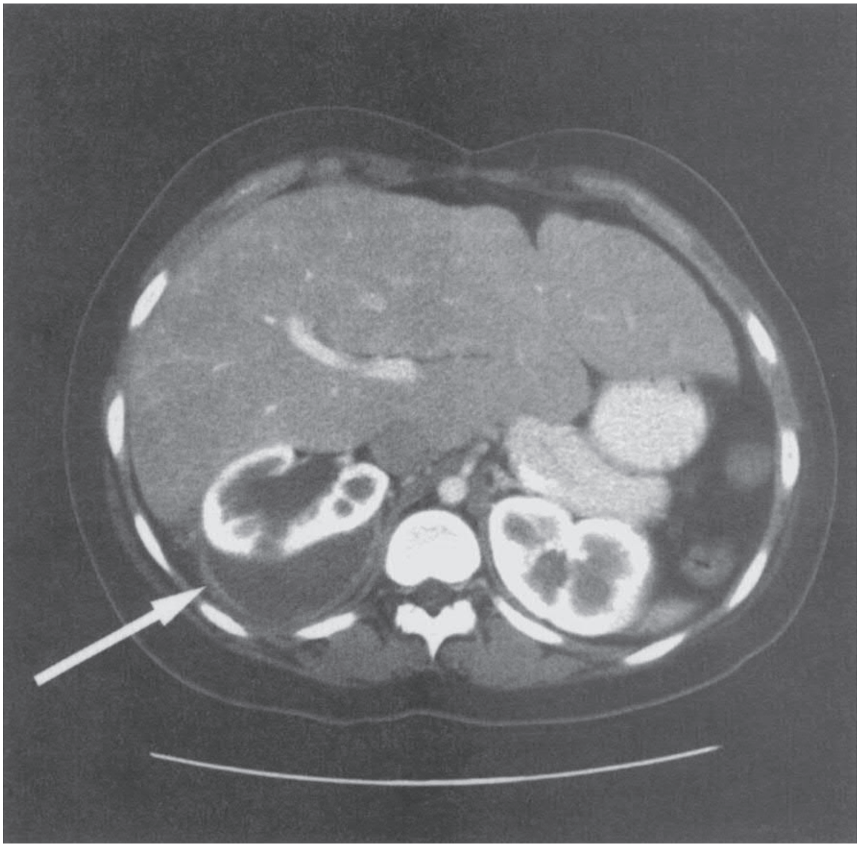
Renal abscesses can be accurately detected using ultrasonography or CT scans. There is a wide gamut of ultrasonographic findings ranging from an anechoic mass within or displacing the kidney, posterior acoustic enhancement, or lack of vascularity on Doppler imaging (Fontanilla et al, 2011). With high sensitivity, CT scans can demonstrate an enlarged kidney with focal areas of hypoattenuation early during the infection. Once the inflammatory wall forms around the fluid collection, the abscess appears as a mass with a rim of contrast enhancement, the "ring" sign (Figure 14–4). CT scans may also demonstrate a wedge-shaped hypodense area of parenchyma, low attenuation (0–20 Hounsfield units [HU]), thickening of Gerota's fascia, stranding of the perinephric fat, or obliteration of the surrounding soft-tissue planes (Dalla Palma et al, 1999; Kawashima et al, 1997). Intravenous pyelogram and kidneys, ureter, and bladder tests are less sensitive in detecting renal/perinephric abscesses, as results are often normal. MRI demonstrates superior tissue resolution, but secondary to cost and motion artifact, it offers little further information than CT scan.

C. Management

The appropriate management of renal abscess must first include appropriate antibiotic therapy. Because it can be difficult to identify the correct causative organisms from the urine or blood, empiric therapy with broad-spectrum antibiotics (ampicillin or vancomycin in combination with an aminoglycoside or third-generation cephalosporin) is usually recommended. If the patient does not respond within 48 hours of treatment, percutaneous drainage under CT scan or ultrasound guidance is indicated, particularly for abscesses >3 cm (Siegel et al, 1996). The drained fluid should be cultured for the causative organisms, and a percutaneous drain should be left indwelling until minimal output is noted and defervescence occurs. If the abscess still does not resolve, then open surgical drainage or nephrectomy may be necessary. Follow-up imaging is needed to confirm resolution of the abscesses. These patients will also require evaluation for underlying urinary tract abnormalities such as stone or obstruction after the infection has resolved.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a form of chronic bacterial infection of the kidney. The affected kidney is almost always hydronephrotic and obstructed. In most cases, XGP occurs unilaterally. Severe inflammation and necrosis obliterate the kidney parenchyma. Characteristically, foamy lipid-laden histiocytes (xanthoma cells) are present and may be mistaken for renal clear cell carcinoma



▲ **Figure 14–4.** Renal abscess. CT scan with intravenous contrast demonstrates a large perinephric fluid collection with rim enhancement (*white arrow*). The parenchyma defect in the right kidney is suggestive of pyelonephritis.

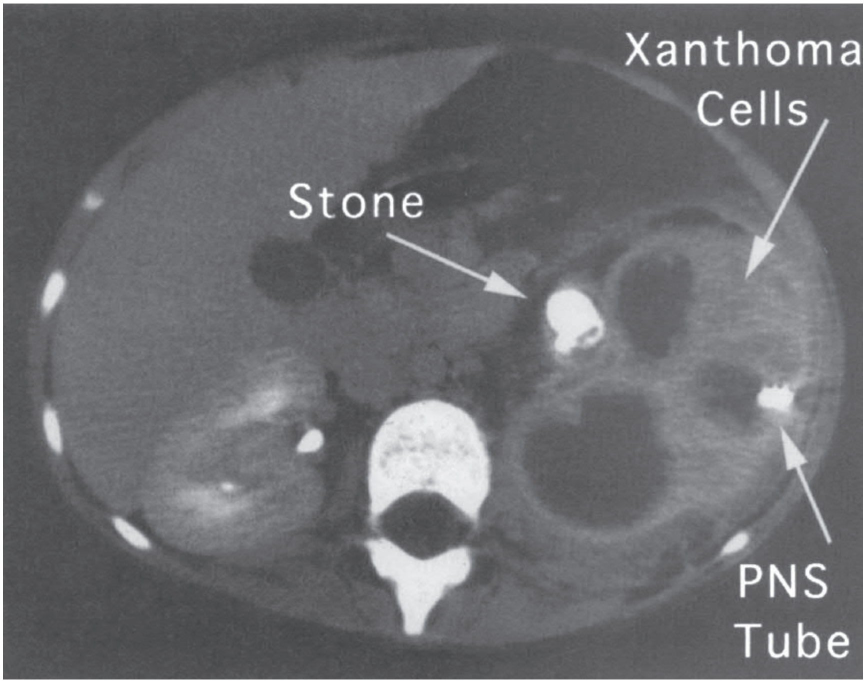
(Iskandar et al, 1993; Lorentzen and Nielsen, 1980). XGP is associated with urinary tract obstruction, infection, nephrolithiasis, diabetes, and/or immunosuppression.

A. Presentation and Findings

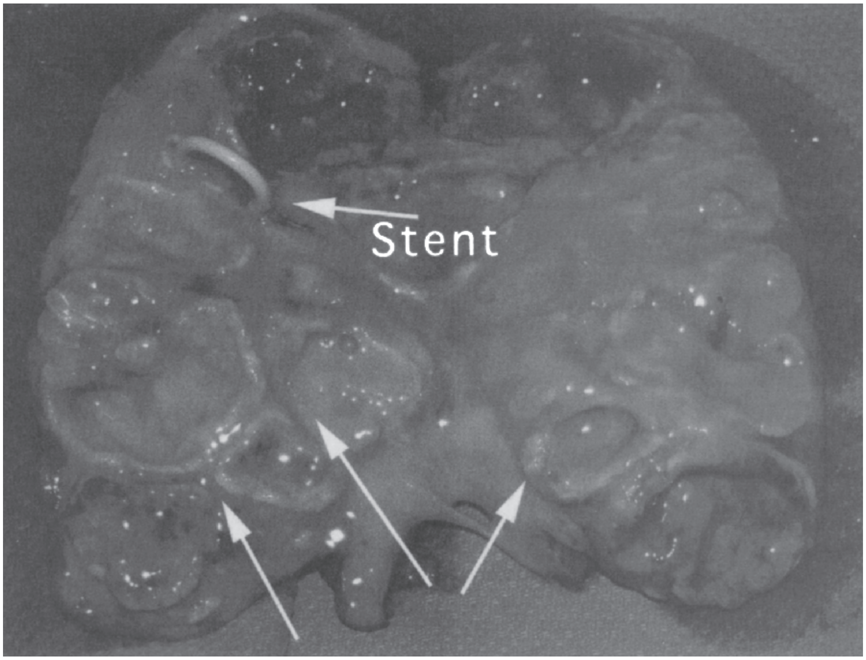
Patients with XGP commonly present with flank pain, fever, chills, and persistent bacteriuria. A history of urolithiasis is present in about 35% of patients (Malek and Elder, 1978). On physical examination, a flank mass can often be palpated. Urinalysis commonly demonstrates leukocytes, bacteria, and proteinuria. Serum blood analysis reveals anemia and may show hepatic dysfunction in approximately 50% of the patients (Kuo et al, 2011). Because XGP occurs primarily unilaterally, azotemia or renal failure is rarely seen (Goodman et al, 1979). *E. coli* or *Proteus* species are commonly cultured from the urine. However, one-third of patients with XGP have no growth in their urine, most likely because they have recently received antibiotic therapy. Approximately 10% of the patients with XGP have mixed organisms or anaerobic bacteria identified in their urine. Culture of the affected renal tissue can reliably identify the causative organism.

B. Radiographic Imaging

Computed tomography scan is the most reliable method in imaging patients suspected of having XGP. It usually demonstrates a large, heterogeneous, nonenhancing reniform mass. The renal parenchyma is often marked with multiple water density lesions, representing dilated calyces or abscesses (Figure 14–5) (Rajesh et al, 2011). On contrast-enhanced images, these lesions will have a prominent blush peripherally, while the central areas, which are filled with pus and debris, do not enhance. The inflammatory process may be seen extending to the perinephric fat, the retroperitoneum, and adjacent organs such as the psoas muscle, spleen, colon, or the great vessels in higher-stage disease. Because of the association of urolithiasis and XGP, renal calculi may be seen (Parsons, 1993). Renal ultrasonography can also be used in performing imaging on patients with XGP, and it usually reveals an enlarged kidney with



A



B

▲ **Figure 14–5.** Xanthogranulomatous pyelonephritis. ***A:*** CT scan demonstrates a large heterogeneous left kidney, with dilated calyces and areas filled with lipid-laden macrophages. Xanthogranulomatous pyelonephritis is often associated with the presence of renal stones. ***B:*** Pathology specimen better demonstrated the pockets of intraparenchymal abscesses and deposition of macrophages (*arrows*) (PNS = percutaneous nephrostomy).

multiple hypoechoic masses, irregular thinned parenchyma, and a dilated collecting system. However, ultrasonography does not provide anatomic details comparable with those obtained from CT scan.

C. Management

The management of XGP is dependent on accurate diagnosis. In some cases, XGP is misdiagnosed as a renal tumor and a nephrectomy is performed and a diagnosis is made pathologically. In those in whom a diagnosis of XGP is suspected, kidney-sparing surgery such as a partial nephrectomy is indicated in focal disease. However, when the infection is diffuse, a nephrectomy with excision of all involved tissue is warranted. There are a handful of reported cases of treating XGP with antibiotic therapy alone (Brown et al, 1996) or in combination with percutaneous drainage; however, these treatments are not likely to be curative in most patients and may lead to complications such as renal cutaneous fistula. Antibiotic treatment should be aimed at the identified organism and usually are sensitive to first-generation cephalosporins, trimethoprim–sulfamethoxazole, aminoglycosides, or fluoroquinolones.

Pyonephrosis

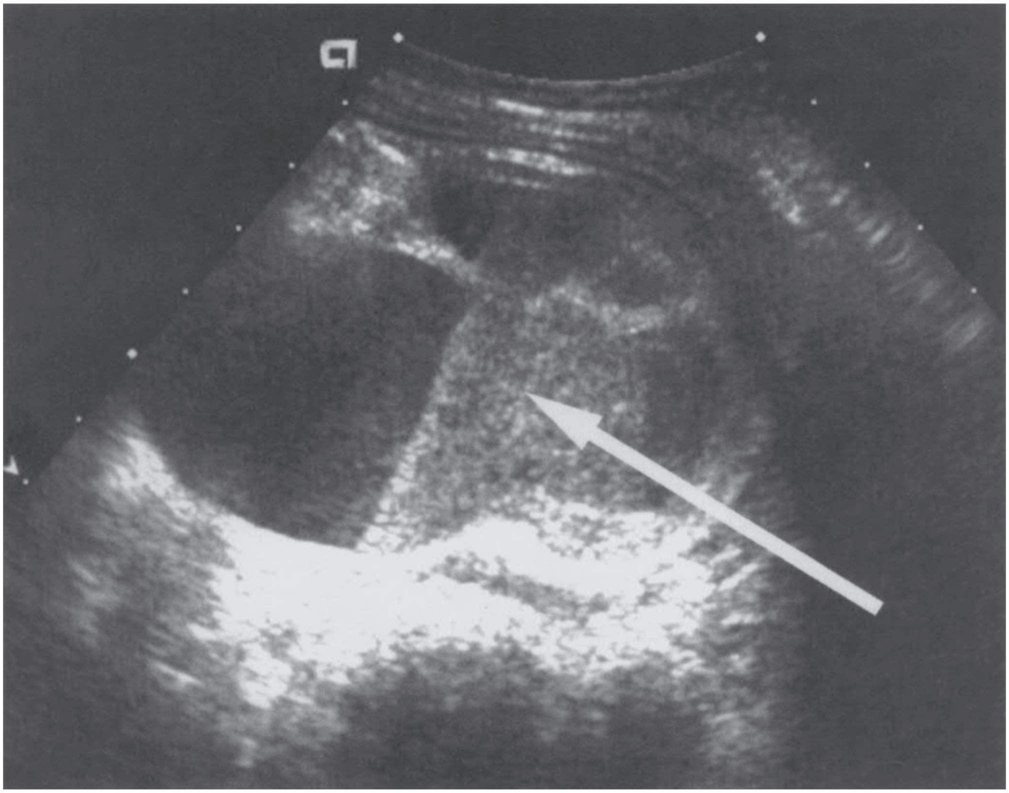
Pyonephrosis refers to bacterial infection of a hydronephrotic, obstructed kidney, which leads to suppurative destruction of the renal parenchyma and potential loss of renal function. Because of the extent of the infection and the presence of urinary obstruction, sepsis may rapidly ensue, requiring rapid diagnosis and management.

A. Presentation and Findings

Patients with pyonephrosis are usually very ill, with high fever, chills, and flank pain. Lower tract symptoms are seldom present. Bacteriuria and pyuria may not be present when there is complete obstruction of the affected kidney.

B. Radiographic Imaging

Imaging with renal ultrasonography can be performed to rapidly diagnose pyonephrosis. Ultrasonographic findings include persistent echoes in the inferior portion of the collecting system, fluid–debris level with dependent echoes that shift with positional changes (Figure 14–6), strong echoes with acoustic shadowing from air in the collecting system,



▲ **Figure 14–6.** Pyonephrosis. Ultrasonography demonstrates fluid–debris level (*white arrow*) within the dilated renal pelvis.

and weak echoes throughout a dilated collecting system. Ultrasonography carries a 90% sensitivity rate and a 97% specificity rate in detection of pyonephrosis from hydronephrosis (Subramanyam et al, 1983). Renal or ureteral calculi may also be identified on ultrasonography. CT scan can give definitive delineation of the point of obstruction and identify other pathology such as retroperitoneal fibrosis or malignancy, which may not be detected on ultrasonography (Wyatt et al, 1995).

C. Management

Management of pyonephrosis includes immediate institution of antibiotic therapy and emergent drainage of the infected collecting system. Broad-spectrum antimicrobials are indicated to prevent sepsis while the causative organism is being identified; antibiotics should be started before manipulation of the urinary tract. Performing drainage of the obstruction through the lower urinary tract (such as using a ureteral stent) should be reserved for patients who are not septic. Extensive manipulation may rapidly induce sepsis and toxemia. In the ill patient, drainage of the collecting system with a percutaneous nephrostomy tube is preferable. Once the infection is treated, additional imaging evaluation is required to identify the cause of the urinary obstruction, such as urolithiasis or ureteropelvic junction obstruction.

BLADDER INFECTION

Acute Cystitis

Acute cystitis refers to urinary infection of the lower urinary tract, principally the bladder. Acute cystitis more commonly affects women than men. The primary mode of infection is ascending from the periurethral/vaginal and fecal flora. The diagnosis is made clinically. In children, the distinction between upper and lower UTI is important. In general, those in whom acute cystitis developed seldom require any extensive radiologic investigation, but those who have febrile UTI require further radiologic studies. Recommendations for children include a screening renal bladder ultrasound and, if abnormal, proceed with voiding cystourethrogram (Roberts, 2011).

A. Presentation and Findings

Patients with acute cystitis present with irritative voiding symptoms such as dysuria, frequency, and urgency. Low back and suprapubic pain, hematuria, and cloudy/foul-smelling urine are also common symptoms. Fever and systemic symptoms are rare. Typically, urinalysis demonstrates WBCs in the urine, and hematuria may be present. Urine culture is required to confirm the diagnosis and identify the causative organism. However, when the clinical picture and urinalysis are highly suggestive of the diagnosis of acute cystitis, urine culture may not be needed. *E. coli* causes most of the acute cystitis with *Proteus, Klebsiella*, and *Enterobacter* spp. following in frequency. Diabetes and lifetime history of UTI are risk factors for acute cystitis.

B. Radiographic Imaging

In uncomplicated infection of the bladder, radiologic evaluation is rarely necessary.

C. Management

Management of acute cystitis consists of a short course of oral antibiotics (reviewed by Falagas et al, 2009). TMP-SMX, nitrofurantoin, and fluoroquinolones have excellent activity against most pathogens that cause cystitis. TMP-SMX and nitrofurantoin are less expensive and thus are recommended for the treatment of uncomplicated cystitis (Huang and Stafford, 2002). However, it is estimated that resistance to TMP-SMX by *E. coli* isolates causing uncomplicated acute cystitis is approximately 20%, compared with <2% to nitrofurantoin (Huang and Stafford, 2002). In adults and children, the duration of treatment is usually limited to 3–7 days dependent on the antibiotic chosen (Gupta et al, 2011). Single-dose therapy has been shown to be effective for fosfomycin and can be offered as a first-line treatment. Resistance to penicillins and aminopenicillins is high, and thus they are not recommended for treatment. In children who have a genitourinary abnormality, such as vesicoureteral reflux, this should be treated as complicated UTI with a longer duration of antimicrobial therapy, usually 10–14 days.

Recurrent Cystitis/UTI

A. Presentation and Findings

Recurrent cystitis/UTI is caused by either bacterial persistence or reinfection with another organism. Identification of the cause of the recurrent infection is important, because the management of bacterial persistence and reinfection are distinct. If bacterial persistence is the cause of recurrent UTI, the removal of the infected source is often curative, whereas preventive therapy is effective in treating reinfection.

B. Radiographic Imaging

When bacterial persistence is the suspected cause, radiologic imaging is indicated. Ultrasonography can be obtained to provide a screening evaluation of the genitourinary tract. More detailed assessment with intravenous pyelogram, cystoscopy, and CT scans may occasionally be necessary. In patients who have frequent, recurrent UTI, bacterial localization studies and more extensive radiologic evaluation (such as retrograde pyelograms) are warranted. When bacterial reinfection is the suspected cause of recurrent cystitis, the patient should be carefully evaluated for evidence of vesicovaginal or vesicoenteric fistula. Otherwise, radiologic examination is rarely necessary in these patients.

C. Management

Management of recurrent cystitis, again, depends on its cause. Surgical removal of the infected source (such as urinary calculi) is needed to treat bacterial persistence. Similarly, fistulas need to be repaired surgically to prevent bacterial reinfection. In most cases of bacterial reinfection, medical management with prophylactic antibiotics is indicated. Low-dose continuous prophylactic antibiotic has been shown to reduce the relative risk for clinical recurrence per patient year to 0.15, favoring antibiotic usage (Albert et al, 2004). Alternatively, intermittent self-start antibiotic therapy can be used in treating recurrent cystitis in some women. Motivated patients self-identify episodes of infection by their symptoms and treat themselves with a single dose of antibiotics such as TMP-SMX. This regimen has been shown to be effective and economical in selected patients with no need for urine culture after self-diagnosis since there is 86–92% rate of positive urine culture in combination with self-diagnosis in appropriately selected patients (Schaeffer et al, 1999; Wong et al, 1985). When the recurrent cystitis/UTI is related to sexual activity, frequent emptying of the bladder and a single dose of antibiotic taken within 2 hours of sexual intercourse can significantly reduce the incidence of recurrent infection (Pfau and Sacks, 1994). Alternatives to antibiotic therapy in the treatment of recurrent cystitis/UTI include intravaginal estriol (Raz and Stamm, 1993), lactobacillus vaginal suppositories (Reid and Burton, 2002), and cranberry juice taken orally (Lowe and Fagelman, 2001).

▶ Malakoplakia

Malakoplakia is an uncommon inflammatory disease of the bladder that can also affect other parts of the urinary tract, including the ureters and kidneys (Stanton and Maxted, 1981). In the bladder, it manifests as friable soft yellow plaques or nodules consisting of large histiocytes (von Hansemann cells) with laminar inclusion bodies (Michaelis–Gutmann bodies) (McClure et al, 1981). Assumed to be caused by defective macrophage killing of bacteria, most commonly *E. coli*, accumulation of the bacterial degradation products leads to the abovementioned nodules (Damjanov and Katz, 1981).

A. Presentation and Findings

Malakoplakia more commonly affects women than men (Stanton and Maxted, 1981) and is associated with a history of UTI. Patients with malakoplakia often are immunosuppressed and include post-organ transplant, AIDS, and malignancy (Damjanov and Katz, 1981). In patients with malakoplakia of the bladder, irritative voiding symptoms (urgency and frequency) and hematuria are common (Curran, 1987). When the disease affects the ureter or kidney, the patient may present with fever, flank pain, or flank mass. When it affects both kidneys, signs or symptoms of azotemia or renal failure may be present (Dobyan et al, 1993).

B. Radiologic Imaging

Radiologic imaging with ultrasonography or CT may demonstrate a mass in the bladder and evidence of obstruction if the disease extends to the ureter (Vas et al, 1985). When the disease involves the kidney, focal or diffuse, hypodense, parenchymal masses may be seen on CT imaging (Frederic et al, 1981). Inclusion of positron emission tomography (PET) scan can be used to diagnose renal involvement with intense uptake of the radiotracer noted (Vanbrabant et al, 2004). MRI can also demonstrate nodules with low T1-weighted, T2-weighted signals (Zimina et al, 2002). It is often difficult to distinguish malakoplakia from malignancy (transitional cell or renal cell carcinoma) with radiologic imaging. The diagnosis is often established after biopsy.

C. Management

Management of malakoplakia consists primarily of antibiotic therapy, especially those that produce high intracellular levels and concentrate in macrophages. Consequently, TMP-SMX and fluoroquinolones are recommended in the treatment of malakoplakia. Treatment with fluoroquinolone has significantly decreased the mortality rate associated with renal malakoplakia (Tam et al, 2003). Bethanecol and ascorbic acid, which enhance phagolysosomal activity by correcting the decreased cGMP levels, may have some benefits (Fudaba et al, 2014). In patients with malakoplakia limited to the lower urinary tract, antibiotic therapy alone usually suffices. However, when malakoplakia involves the ureter or kidney, surgical excision may be needed in addition to the antibiotic therapy (Dasgupta et al, 1999; Long and Althausen, 1989). The prognosis is poor, and the mortality rate is high in patients who have bilateral renal involvement, regardless of treatment.

PROSTATE INFECTION

▶ Acute Bacterial Prostatitis

Acute bacterial prostatitis refers to inflammation of the prostate associated with a UTI. It is believed that infection results from ascending urethral infection or reflux of infected urine from the bladder into the prostatic ducts. In response to bacterial invasion, leukocytes (polymorphonuclear leukocytes, lymphocytes, plasma cells, and macrophages) are seen within and surrounding the acini of the prostate. Edema and hyperemia of the prostatic stroma frequently develop. With prolonged infection, variable degrees of necrosis and abscess formation can occur.

A. Presentation and Findings

Acute bacterial prostatitis is uncommon in prepubertal boys but frequently affects adult men. It is the most common urologic diagnosis in men younger than 50 years and third most common in men older than 50 years (Collins et al, 1998).

Patients with acute bacterial prostatitis usually present with an abrupt onset of constitutional (fever, chills, malaise, arthralgia, myalgia, lower back/rectal/perineal pain) and urinary symptoms (frequency, urgency, dysuria). They may also present with urinary retention due to swelling of the prostate. Digital rectal examination reveals a tender, enlarged gland that is irregular and warm. Urinalysis usually demonstrates WBCs and occasionally hematuria. Serum blood analysis typically demonstrates leukocytosis. Prostate-specific antigen levels are often elevated. The diagnosis of prostatitis is made with microscopic examination and culture of the prostatic expressate and culture of urine obtained before and after prostate massage. In patients with acute prostatitis, fluid from the prostate massage often contains leukocytes with fat-laden macrophages. However, at the onset of acute prostatitis, prostatic massage is seldom suggested because the prostate is quite tender and the massage may lead to bacteremia. Similarly, urethral catheterization should be avoided. Culture of urine and prostate expressate usually identifies a single organism, but occasionally, polymicrobial infection may occur. *E. coli* is the most common causative organism in patients with acute prostatitis. Other Gram-negative bacteria (*Proteus, Klebsiella, Enterobacter, Pseudomonas*, and *Serratia* spp.) and enterococci are less frequent pathogens (Kanamaru et al, 2006). Risk factors include phimosis, unprotected anal intercourse, acute epididymitis, indwelling Foley catheter, and recent transrectal ultrasound-guided prostate biopsy (TRUS).

B. Radiologic Imaging

Radiologic imaging is rarely indicated in patients with acute prostatitis unless there is failure to improve after antibiotic therapy. Bladder ultrasonography may be useful in determining the amount of residual urine. Transrectal ultrasonography is indicated only in patients who do not respond to conventional therapy to evaluate for possible abscess formation.

C. Management

Treatment with antibiotics is essential in the management of acute prostatitis. Empiric therapy directed against Gram-negative bacteria and enterococci should be instituted immediately while awaiting the culture results. Trimethoprim and fluoroquinolones have high drug penetration into prostatic tissue and are recommended for 4–6 weeks (Wagenlehner et al, 2005). Concern for fluoroquinolone drug resistance is rising, particularly in patients who have undergone TRUS biopsy, and local antibiograms should be utilized to help direct antibiotic therapy (Nagy and Kubej, 2012). The long duration of antibiotic treatment is intended to allow complete sterilization of the prostatic tissue to prevent complications such as chronic prostatitis and abscess formation (Childs, 1992; Nickel, 2000). Patients who have sepsis, are immunocompromised or in acute urinary retention, or have significant medical comorbidities would benefit from hospitalization and treatment with parenteral antibiotics. Ampicillin and an aminoglycoside provide effective therapy against both Gram-negative bacteria and enterococci. Patients with urinary retention secondary to acute prostatitis should be managed with a suprapubic catheter because transurethral catheterization or instrumentation is contraindicated.

Chronic Bacterial Prostatitis

In contrast to the acute form, chronic bacterial prostatitis has a more insidious onset, characterized by relapsing, recurrent UTI caused by the persistence of pathogen in the prostatic fluid despite antibiotic therapy.

A. Presentation and Findings

Most patients with chronic bacterial prostatitis typically present with dysuria, urgency, frequency, nocturia, and low back/perineal pain. These patients usually are afebrile and commonly have a history of recurrent or relapsing UTI, urethritis, or epididymitis caused by the same organism (Nickel and Moon, 2005). Others are asymptomatic, but the diagnosis is made after investigation for bacteriuria. In patients with chronic bacterial prostatitis, digital rectal examination of the prostate is often normal; occasionally, tenderness, firmness, or prostatic calculi may be found on examination. Urinalysis demonstrates a variable degree of WBCs and bacteria in the urine, depending on the extent of the disease. Serum blood analysis rarely shows any evidence of leukocytosis. Prostate-specific antigen (PSA) levels may be elevated. Diagnosis is made after identification of bacteria from prostate expressate or urine specimen after a prostatic massage, using a midstream urine collection sample. The causative organisms are similar to those of acute bacterial prostatitis. It is currently believed that other Gram-positive bacteria—*Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*—can be a cause of chronic bacterial prostatitis but are difficult to culture in standard conditions.

B. Radiologic Imaging

Radiologic imaging is rarely indicated in patients with chronic prostatitis. Transrectal ultrasonography is indicated only if a prostatic abscess is suspected.

C. Management

Antibiotic therapy is similar to that for acute bacterial prostatitis (Bjerklund et al, 1998). Interestingly, the presence of leukocytes or bacteria in the urine and prostatic massage does not predict antibiotic response in patients with chronic prostatitis (Nickel et al, 2001). Using fluoroquinolones, some patients may respond after 4–6 weeks of treatment, but relapse is not uncommon, requiring the duration of antibiotic therapy to be extended to 3–4 months. TMP-SMX is the cheaper option, but in patients younger than 35 years, fluoroquinolones offer activity against both gonorrheal and chlamydial organisms. The addition of an α-blocker and anti-inflammatory agents to antibiotic therapy has been shown to reduce symptom recurrence in patients with chronic pelvic pain syndrome (Anothaisintawee et al, 2011). Despite maximal therapy, cure is rarely achieved, due to poor penetration of antibiotic into prostatic tissue and relative isolation of the bacterial foci within the prostate. Third-line agents include 5α-reductase inhibitors, glycosaminoglycans, quercetin, cernilton (CN-009), and saw palmetto. A double-blind, randomized, placebo-controlled study evaluated patients with chronic prostatitis and pelvic pain syndrome and utilized transurethral intraprostatic injection of Botox, which reduced pain and symptoms by 80% at 6 months (Falahatkar et al, 2014). When recurrent episodes of infection occur despite antibiotic therapy, suppressive antibiotic (TMP-SMX, one single-strength tablet daily, nitrofurantoin 100 mg daily, or ciprofloxacin 250 mg daily) may be used (Meares, 1987). Transurethral resection of the prostate has been used to treat patients with refractory disease; however, the success rate has been variable, and this approach is seldom recommended (Barnes et al, 1982).

Granulomatous Prostatitis

Granulomatous prostatitis is an uncommon form of prostatitis. It can result from bacterial, viral, or fungal infection; the use of bacille Calmette–Guérin (BCG) therapy; malakoplakia; or systemic granulomatous diseases affecting the prostate (Srigley, 2004). Two-thirds of the cases have no specific cause. There are two distinct forms of nonspecific granulomatous prostatitis: noneosinophilic and eosinophilic. The former represents an abnormal tissue response to extravasated prostatic fluid (O'Dea et al, 1977). The latter is a more severe, allergic response of the prostate to some unknown antigen.

A. Presentation and Findings

Patients with granulomatous prostatitis often present acutely, with fever, chills, hematuria, and obstructive/irritative voiding symptoms. Some may present with urinary retention. Patients with eosinophilic granulomatous prostatitis are severely ill and have high fevers. Digital rectal examination in patients with granulomatous prostatitis demonstrates a hard, indurated, and fixed prostate, which is difficult to distinguish from prostate carcinoma. Urinalysis and culture do not show any evidence of bacterial infection. Serum blood analysis typically demonstrates leukocytosis; marked eosinophilia is often seen in patients with eosinophilic granulomatous prostatitis. The diagnosis is made after biopsy of the prostate.

B. Management

Some patients respond to antibiotic therapy, corticosteroids, and temporary bladder drainage. Those with eosinophilic granulomatous prostatitis respond dramatically to corticosteroids (Ohkawa et al, 2001). Transurethral resection of the prostate may be required in patients who do not respond to treatment and who have significant outlet obstruction. It should be noted that patients with asymptomatic post-BCG granulomatous prostatitis do not require treatment.

Prostate Abscess

Most cases of prostatic abscess result from complications of acute bacterial prostatitis that were inadequately or inappropriately treated. Prostatic abscesses are often seen in patients with diabetes; those receiving chronic dialysis; or patients who are immunocompromised, undergoing urethral instrumentation, or who have chronic indwelling catheters.

A. Presentation and Findings

Patients with prostatic abscess present with symptoms similar to those with acute bacterial prostatitis. Typically, these patients were treated for acute bacterial prostatitis previously and had a good initial response to treatment with antibiotics. However, their symptoms recurred during treatment, suggesting development of prostatic abscesses. On digital rectal examination, the prostate is usually tender and swollen. Fluctuance is seen in only 16% of patients with prostatic abscess (Weinberger et al, 1988).

B. Radiologic Imaging

Imaging with transrectal ultrasonography (Figure 14–7) or pelvic CT scan is crucial for diagnosis and treatment.

C. Management

Antibiotic therapy in conjunction with drainage of the abscess is required. Transrectal ultrasonography or CT scan can be used to direct transrectal drainage of the abscess (Barozzi et al, 1998). Transurethral resection and drainage may be required if transrectal drainage is inadequate and is recommended when the abscess is larger than 1 cm. When properly diagnosed and treated, most cases of prostatic abscess resolve without significant sequelae (Weinberger et al, 1988).

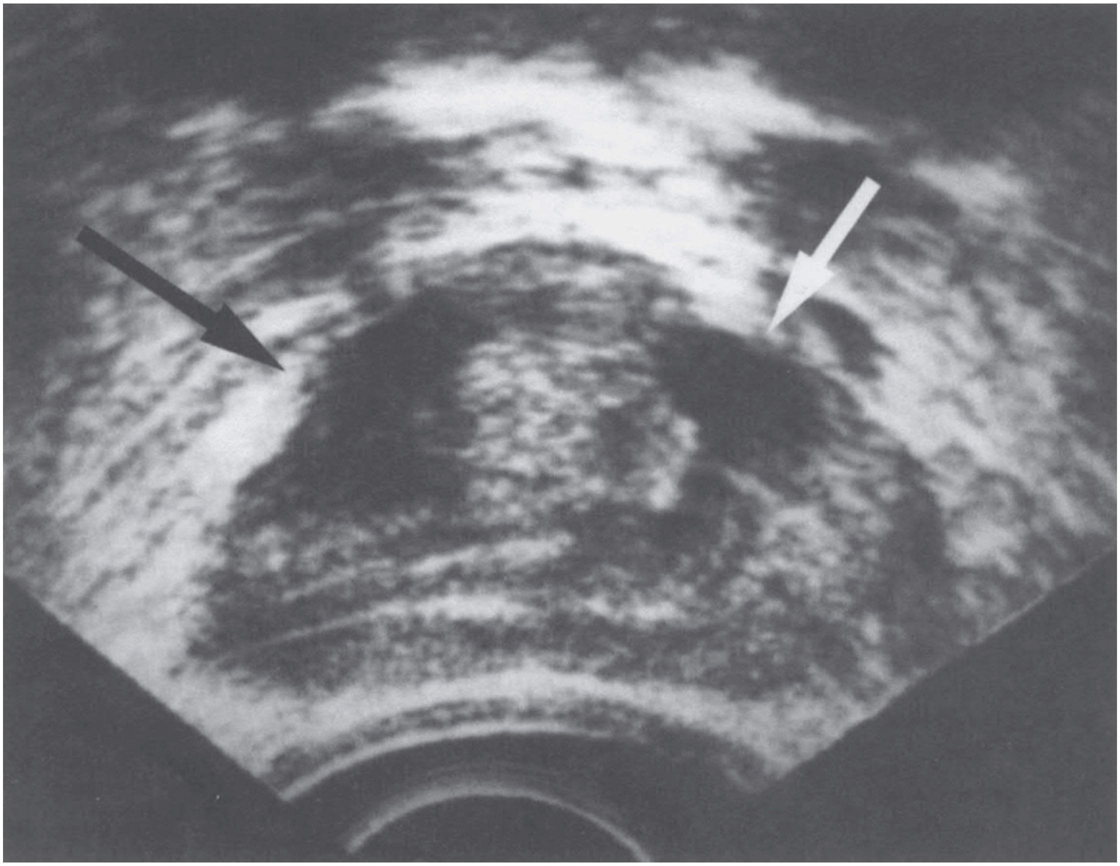
URETHRITIS

Types of Urethritis

Infection/inflammation of the urethra can be categorized into those types caused by *Neisseria gonorrhoeae* (GU) and by other organisms (NGU–*Chlamydia trachomatis, Ureaplasma urealyticum*, *Trichomonas vaginalis*, and herpes simplex virus) (Dixon et al, 2002). Most cases are acquired during sexual intercourse.

A. Presentation and Findings

Patients with urethritis may be completely asymptomatic (up to 75% of patients) or present with urethral discharge and dysuria. The amount of discharge may vary significantly, from profuse to scant amounts. Obstructive voiding



▲ **Figure 14–7.** Prostatic abscess. Transrectal ultrasonography demonstrates hypoechoic lesions (*black and white arrows*) in the prostate consistent with abscesses.

symptoms are present primarily in patients with recurrent infection, in whom urethral strictures subsequently develop. The diagnosis is made from examination and culture of the urethra or the first-voided urine specimen by nucleic acid amplification tests or PCR. Approximately 30% of men infected with *N. gonorrhoeae* will have concomitant infection with *C. trachomatis*.

B. Radiologic Imaging

Retrograde urethrography is indicated only in patients with recurrent infection and obstructive voiding symptoms. Most patients with uncomplicated urethritis do not require any radiologic imaging.

C. Management

Pathogen-directed antibiotic therapy is required. In patients with gonococcal urethritis, azithromycin, in a single 2-g dose, should be used as it treats both GU and NGU, which often exist concomitantly. Intramuscular ceftriaxone can be used for isolated GU. For patients with nongonococcal urethritis, treatment is with tetracycline or erythromycin (500 mg 4 times daily) or doxycycline (100 mg twice daily) for 7–14 days (O'Mahony, 1999). However, the most essential component of treatment is prevention. Sexual partners of the affected patients should be treated, and protective sexual practices (such as using condoms) are recommended.

EPIDIDYMITIS/ORCHITIS

▶ Causes of Epididymitis/Orchitis

Infection and inflammation of the epididymis most often result from an ascending infection from the lower urinary tract. The infection in the epididymis may spread to involve the testis. Most cases of epididymitis/orchitis in men younger than 35 years are due to sexually transmitted organisms (*N. gonorrhoeae* and *C. trachomatis*) in over

50% of cases; those in children and older men are due to urinary pathogens such as *E. coli*, *Pseudmonas*, *and Proteus* spp. Children rarely have a positive urine culture, and other causes of epididymitis/orchitis in young children are due to a postinfectious inflammatory reaction to pathogens such as *Mycoplasma pneumoniae*, enteroviruses, and adenoviruses. In addition, congenital abnormalities or functional voiding problems may lead to urinary reflux into the ejaculatory ducts, leading to a predilection for chemical epididymitis, which often follows a more benign course (Raveenthiran and Sam, 2011). Therefore, epididymitis/orchitis can be of infectious etiology or chemical/irritative in nature. In homosexual men who practice anal intercourse, *E. coli* and other coliform bacteria are common causative organisms. Other rare causes of epididymitis include Behcet syndrome, Henoch–Schonlein purpura, sarcoidosis, or amiodarone-induced epididymitis.

A. Presentation and Findings

Patients with epididymitis/orchitis present with gradually worsening, severe scrotal pain that may radiate to the groin or flank. Scrotal enlargement due to the inflammation of the epididymis/testis or a reactive hydrocele may develop rapidly. Other symptoms of urethritis, cystitis, or prostatitis may be present before or concurrent with the onset of scrotal pain. On physical examination, an enlarged and red scrotum is present, and it is often difficult to distinguish the epididymis from the testis during the acute infection. Normal cremasteric reflex is noted, unlike in testicular torsion. A thickened spermatic cord can occasionally be palpated. Urinalysis typically demonstrates WBCs and bacteria in the urine or urethral discharge. Serum blood analysis often reveals leukocytosis.

B. Radiologic Imaging

Frequently, it is difficult to distinguish epididymitis from acute testicular torsion from the history and physical examination alone (Petrack and Hafeez, 1992). Scrotal Doppler ultrasonography or radionuclide scanning can be used to confirm the diagnosis with 92–100% sensitivity for epididymitis (Yu et al, 2012). The presence of blood flow in the testis on Doppler ultrasonography or uptake of the tracers into the center of the testis on radionuclide scanning rules out torsion. On scrotal ultrasonography, patients with epididymitis/orchitis commonly have an enlarged epididymis or testis with increased blood flow. A reactive hydrocele may also be seen. Prepubertal children who are diagnosed with epididymitis will require radiologic investigation with a renal and bladder ultrasound (RBUS) and voiding cystourethrogram (VCUG) to assess for urinary tract anomalies such as reflux or ureteral ectopia (Likitnukul et al, 1987). Postpubertal children who are diagnosed with epididymitis should be educated about sexually transmitted diseases and safe sexual practices.

C. Management

Oral antibiotic treatment is directed against specific causative organisms, as mentioned in the previous sections on urethritis and UTI. In addition, bed rest, scrotal elevation, and the use of nonsteroidal anti-inflammatory agents are helpful in reducing the duration of the symptoms. In patients with epididymitis/orchitis caused by sexually transmitted organisms, treatment of their sexual partners is recommended to prevent reinfection. For patients with sepsis or severe infection, hospitalization and parenteral antibiotic therapy may be needed. Open drainage is indicated in cases in which an abscess develops. Occasionally, patients with chronic, relapsing epididymitis and scrotal pain may require epididymectomy/orchiectomy for relief of their symptoms.

SPECIAL CIRCUMSTANCES

UTI Related to Pregnancy

With pregnancy, there are anatomic and physiologic changes to the urinary tract due to compression by the gravid uterus and alterations in the hormonal milieu. Renal length increases by approximately 1 cm during normal pregnancy as a result of increased vascular and interstitial volume (Waltzer, 1981). The glomerular filtration rate increases by 30–50%, most likely secondarily to the increase in cardiac output (Waltzer, 1981). Typically, there is significant ureteral dilation with resultant urinary stasis during the second and third trimesters of gestation. This hydroureter is attributed to the smooth-muscle-relaxing effects of progesterone and the mechanical compression of the ureters by the uterus at the level of the pelvic brim (Waltzer, 1981). The bladder is also affected, both physically and physiologically. The enlarged uterus displaces the bladder superiorly and anteriorly.

Because of these changes in the urinary tract during normal pregnancy, bacteriuria is a clinically relevant finding in pregnant women. It is estimated that the prevalence of asymptomatic bacteriuria (ASB) is 5–10%, which is not significantly different from that in nonpregnant women of comparable age. ASB occurs most commonly between 9 and 17 weeks of gestation with risk factors including increasing age and parity, diabetes, sickle cell disease, and structural abnormalities. Interestingly, only 2–4% of pregnant women will develop pyelonephritis (ACOG, 2008). About 60–70% of the episodes of pyelonephritis occur during the second and third trimesters of pregnancy, when urinary stasis is the greatest. In 10–20%, recurrent episodes of pyelonephritis develop before delivery (Gilstrap et al, 1981). When left untreated, pyelonephritis during pregnancy is associated with a high rate of infant prematurity and its associated perinatal mortality (Locksmith and Duff, 2001; McGregor and French, 1998; Schieve et al, 1994). It remains unclear whether treated pyelonephritis during pregnancy has any effect on the developing fetus (Gilstrap and Ramin, 2001).

Table 14–9. Antibiotics and their effects on the developing fetus.

Drugs	Fetal side effects
Sulfonamides	Kernicterus
Trimethoprim	Interferes with neural tube development
Tetracyclines	Dysplasia and discoloration of teeth and bones
Nitrofurantoin	Hemolysis and G6PD deficiency in third trimester, otherwise safe for first- and second-trimester use
Aminoglycosides	Nerve damage
Fluoroquinolones	Interferes with cartilage formation
Penicillins	Safe
Cephalosporins	Safe
β-Lactamase inhibitors	Safe
Monobactams	Safe
Fosfomycin trometamol	Safe

Consequently, it is recommended that women be screened for asymptomatic bacteriuria during pregnancy to prevent the development of pyelonephritis. A voided urine specimen should be obtained at the first prenatal visit and during the third trimester. For asymptomatic individuals, significant bacteriuria is defined as two voided urine cultures with $>10^5$ CFU/mL of a single organism. For symptomatic pregnant women, $>10^3$ CFU/mL is considered significant (Rubin et al, 1992). Pregnant women who are found to have bacteriuria should be treated with penicillins, oral cephalosporins (Christensen, 2000; Wing et al, 1999), or fosfomycin trometamol (Minassian et al, 1998). Of note, nitrofurantoin can be utilized in the first and second trimesters of pregnancy but should be avoided in the third trimester secondary to hemolytic risks. Table 14–9 lists the antibiotics and their effects on pregnancy. Repeat urine culture to document eradication of bacteriuria is necessary in all patients. Patients with acute bacterial pyelonephritis should be treated with parenteral cephalosporins, penicillins with β-lactamase inhibitors, or monobactams (Rubin et al, 1992). Periodic surveillance urine culture is recommended because many of these women will have recurrent episodes of pyelonephritis.

UTI in Patients with Human Immunodeficiency Virus or Acquired Immunodeficiency Syndrome

Human immunodeficiency virus (HIV) alters the normal host defense against bacterial infection. When the CD4 lymphocyte count falls to $<200\ \text{mm}^{-3}$, the risk of bacterial and opportunistic fungal UTI increases dramatically (Evans et al, 1995; Hoepelman et al, 1992). In addition, antiretroviral medications used to treat HIV (eg, zidovudine) can further suppress normal immune response and increase the risk of UTI in these patients. Atypical infections include *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, and *mycobacteria* spp. (Lebovitch and Mydlo, 2008).

A. UTI/Cystitis

Hoepelman et al (1992) obtained urine cultures from HIV-positive men prospectively and when they had symptoms suggestive of a UTI. They observed that positive urine cultures were identified in 30% of HIV-infected men with CD4 $< 200\ \text{mm}^{-3}$ and in 11% with CD4 = 200–500 mm^{-3}, while none with CD4 $> 500\ \text{mm}^{-3}$ had evidence of a urine infection. Gugino et al (1998) similarly observed that the incidence of bacteriuria in asymptomatic HIV-infected women was the same as that in uninfected women. Because of the common prophylactic use of TMP-SMX to prevent *Pneumocystis carinii* pneumonia in AIDS patients, the incidence of UTI in this group is decreased.

B. Prostatitis

In HIV patients, the incidence of bacterial prostatitis is approximately 3%, and it is 14% in patients with AIDS, compared with 1–2% in noninfected men of similar age (Leport et al, 1989). Causative organisms include common prostatitis pathogens such as *E. coli* and *Proteus* spp. and other less common organisms such as *Salmonella typhi*, *S. aureus*, *P. aeruginosa, and N. gonorrhoeae* (Staiman and Lowe, 1995). Prolonged treatment (4–6 weeks) with fluoroquinolones may be necessary because of a high risk of reinfection and lower immunity status in these patients. Prostatic abscess is more common in patients with AIDS compared with that in the general population (Staiman and Lowe, 1995; Trauzzi et al, 1994). Causative organisms include *E. coli* and other Gram-negative bacteria or opportunistic fungus or mycobacterial infection (Lee et al, 2001). Effective drainage and prolonged antimicrobial or antifungal therapy are needed.

C. Epididymitis and Urethritis

In HIV-infected men, epididymitis may be caused by *N. gonorrhoeae* and *C. trachomatis*. However, infection by coliform bacteria such as *E. coli* is more common, especially in patients having unprotected anal intercourse (Berger et al, 1987). In HIV-infected patients with suppurative or antibiotic-resistant epididymitis, infection with fungi or mycobacteria should be considered (Desmond et al, 1993). In HIV-infected men who present with urethritis, treatment for both *Chlamydia* and *N. gonorrhoeae* is indicated even when gonococcus is isolated only from culture secondary to the high coinfection rate. Because of the increased viral shedding with genital infections, it is recommended that HIV-infected patients abstain from sexual intercourse until 7 days after treatment is completed.

D. Infection by Uncommon Organisms

Urinary infection with *Mycobacterium* species can develop in HIV-infected patients. The kidneys are first infected and the infection spreads to the lower urinary tract. In patients with AIDS, it is estimated that 6–23% have renal tuberculosis, based on renal tissue biopsy during necropsy (Marques et al, 1996). *M. tuberculosis* is the most common pathogen; *Mycobacterium avium and Mycobacterium intracellulare* are less common (Sepkowitz et al, 1995). In HIV-infected patients who present with irritative/obstructive voiding symptoms but have no evidence of bacterial infection on culture, infection of the lower urinary tract by *Mycobacterium* species should be considered. Few patients present with hematuria or sterile pyuria (Marques et al, 1996). Treatment with at least two antituberculosis agents is needed for 6–9 months, which can improve proteinuria and renal function as noted by Nourse and colleagues when children with HIV and disseminated tuberculosis were evaluated (Nourse et al, 2010).

▶ UTIs in Patients with Diabetes Mellitus

Urinary tract infections are more common and tend to have a more complicated course in patients with diabetes mellitus with increasing susceptibility with the longer disease duration and worsening diabetic severity (reviewed by Chen et al, 2009). There is a two- to fivefold increase in the incidence of acute pyelonephritis in diabetic patients compared with nondiabetic patients. Complications such as emphysematous pyelonephritis and renal and perirenal abscesses are more frequently seen in the diabetic patients (Williams and Schaeffer, 2004). Interestingly, the mortality and risk of hospitalization for UTI were not increased in patients with diabetes; however, the length of hospitalization may be prolonged. Asymptomatic bacteriuria occurs in diabetic women more commonly than in nondiabetics. It is associated with an increased risk of UTI among patients with type 2 diabetes. However, treatment of asymptomatic bacteriuria with antimicrobial therapy has not been shown to reduce symptomatic UTIs, pyelonephritis, or hospitalization for UTI (Ooi et al, 2004).

The risk for UTI correlated with the degree of glycemia as measured by HBA_{1c}. Autonomic neuropathy resulting in dysfunctional voiding and urinary retention can prevent bacterial clearance through micturition and thereby promote bacterial growth. Defects in the local urinary cytokine secretions and an increased adherence of the microorganisms to the uroepithelial cells are also potential mechanisms that may contribute to the increased prevalence of both asymptomatic and symptomatic bacteriuria in these patients (Hoepelman et al, 2003; Nicolle, 2005). Elevated glucose levels in the urine can cause neutrophil dysfunction and impede phagocytosis, leading to decreased clearance of bacteria, therefore allowing bacterial invasion and subsequent UTI (Johnsson et al, 2013). No relationship between specific uropathogen prevalence and diabetes status has been found; however, diabetic patients with asymptomatic bacteriuria are more likely to be infected by *Klebsiella* and *Enterococcus* than by *E. coli*.

Although resistant bacteria are more frequently found in diabetic patients with UTI, empiric treatment with antibiotic therapy for a diabetic patient with complicated UTIs is similar to that of the nondiabetic patient. One important exception is that staphylococcal infection is not uncommon in diabetic patients and can lead to urinary tract sepsis. This should be considered especially when a diabetic patient presents with a renal carbuncle. Oral outpatient therapy is not recommended for the diabetic patient with a complicated UTI. Treatment with TMP-SMX should be avoided if possible, because it can potentiate the hypoglycemic effects of the oral hypoglycemic drugs. Fluoroquinolones are safe and effective (ie, have low resistance) in the treatment of diabetic patients with complicated UTIs (Williams and Schaeffer, 2004).

▶ Asymptomatic Bacteriuria in Catheterized Patients

Patients with indwelling Foley catheters or suprapubic cystotomy tubes and those performing clean intermittent catheterization present a unique challenge. Most of these patients will have a positive urine culture or urinalysis when sampled, but the question remains when to treat the patient. Bacteriuria is established secondary to biofilm formation and bacteria that ascend into the bladder and establishes presence within 72 hours of catheter placement. The Infectious Disease Society of America guidelines have proposed strategies to reduce antibiotic resistance and do not recommend antimicrobial treatment in asymptomatic bacteriuria patients with indwelling catheters. In the event of a febrile UTI with a positive culture, the recommendations are to treat. In spinal cord patients who may not be sensate, other symptoms that must be relied on include leakage around the catheter or between catheterizations, foul-smelling urine, suprapubic pressure, increasing muscle spasticity, fever, and costovertebral angle tenderness (Nicolle, 2012). In the event of a urine culture returning with *Proteus* spp., regardless of whether there are symptoms noted, recommended treatment for these patients is antimicrobial therapy for 10–21 days as there is a chance of upper tract deterioration in the future secondary to urolithiasis development (Franz and Horl, 1999). If stones are present, surgical removal is required to clear the bacterial nidus.

BIBLIOGRAPHY

Abad CL, Safdar N: The role of lactobacillus probiotics in the treatment or prevention of urogenital infections—a systematic review. J Chemother 2009;21(3):243–252.

ACOG (American College of Obstetricians and Gynecologists): ACOG Practice Bulletin 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol 2008;111:785–794.

Al-Orifi F et al: Urine culture from bag specimens in young children: Are the risks too high? J Pediatr 2000;137:221.

Albert X, Huertas I, Pereiró II, et al: Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev 2004:CD001209.

Anderson GG et al: Host subversion by formation of intracellular bacterial communities in the urinary tract. Microbes Infect 2004; 6(12):1094–1101.

Anonymous: Superbug E. coli found for just second time in US, 2016 (available online at: http://abcnews.go.com/Health/superbug-coli-found-time-us/story?id=40488140), ABC News.

Anothaisintawee T, Attia J, Nickel JC, et al: Management of chronic prostatitis/chronic pelvic pain syndrome: A systematic review and network meta-analysis. JAMA 2011;305(1):78–86.

Badalato G, Kaufmann M: Adult UTI. AUA Medical Student Curriculum, 2016.

Barnes RW et al: Transurethral resection of the prostate for chronic bacterial prostatitis. Prostate 1982;3:215.

Barozzi L et al: Prostatic abscess: Diagnosis and treatment. Am J Roentgenol 1998;170:753.

Baskin L, Cooper C, Copp H: Infections, Pediatric Urology. AUA Core Curriculum, 2016.

Berger RE et al: Etiology and manifestations of epididymitis in young men: Correlations with sexual orientation. J Infect Dis 1987;155:1341.

Bjerklund Johansen TE et al: The role of antibiotics in the treatment of chronic prostatitis: A consensus statement. Eur Urol 1998; 34:457.

Bjorksten B, Kaijser B: Interaction of human serum and neutrophils with *Escherichia coli* strains: Differences between strains isolated from urine of patients with pyelonephritis or asymptomatic bacteriuria. Infect Immun 1978;22:308.

Blanco M et al: Virulence factors and O groups of *Escherichia coli* isolates from patients with acute pyelonephritis, cystitis and asymptomatic bacteriuria. Eur J Epidemiol 1996;12:191.

Bortolussi R et al: Capsular K1 polysaccharide of *Escherichia coli*: Relationship to virulence in newborn rats and resistance to phagocytosis. Infect Immun 1979;25:293.

Bower JM et al: Covert operations of uropathogenic *Escherichia coli* within the urinary tract. Traffic 2005;6(1):951–954.

Brown PD et al: Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. Clin Infect Dis 2002;34:1061.

Brown PS Jr et al: Xanthogranulomatous pyelonephritis: Report of nonsurgical management of a case and review of the literature. Clin Infect Dis 1996;22:308.

Carapetis JR et al: Randomized, controlled trial comparing once daily and three times daily gentamicin in children with urinary tract infections. Pediatr Infect Dis J 2001;20:240.

Chaudhari P, Monuteaux M, Bachur R: Urine concentration and pyuria for identifying UTI in infants. Pediatrics 2016;138(5).

Chen MT et al: Percutaneous drainage in the treatment of emphysematous pyelonephritis: 10-year experience. J Urol 1997; 157:1569.

Chen SL et al: Diabetes mellitus and urinary tract infection: Epidemiology, pathogenesis and proposed studies in animal models. J Urol 2009;182(6 Suppl):S51–S56.

Childs S: Current diagnosis and treatment of urinary tract infections. Urology 1992;40:295.

Chiou YY et al: Renal fibrosis: Prediction from acute pyelonephritis focus volume measured at 99mTc dimercaptosuccinic acid SPECT. Radiology 2001;221:366–370.

Chowdhury P et al: Minireview: Functions of the renal tract epithelium in coordinating the innate immune response to infection. Kidney Int 2004;66(4):1334–1344.

Collins MM et al: How common is prostatitis? A national survey of physician visits. J Urol 1998;159:1224.

Connell I et al: Type 1 fimbrial expression enhances *Escherichia coli* virulence for the urinary tract. Proc Natl Acad Sci USA 1996; 93:9827.

Conway PH, Cnaan A, Zaoutis T, et al: Recurrent urinary tract infections in children: Risk factors and association with prophylactic antimicrobials. JAMA 2007;298:179.

Copp H, Yiee J, Smith A, et al: Use of urine testing in outpatients treated for urinary tract infection. Pediatrics 2013;132(3).

Costelloe C et al: Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. BMJ 2010;18:34.

Curran FT: Malakoplakia of the bladder. Br J Urol 1987;59:559.

Czaja CA, Scholes D, Hooton TM, Stamm WE: Population-based epidemiologic analysis of acute pyelonephritis. Clin Infect Dis 2007;45(3):273–280.

Dacher JN et al: Rational use of CT in acute pyelonephritis: Findings and relationships with reflux. Pediatr Radiol 1993;23:281.

Dalla Palma L et al: Medical treatment of renal and perirenal abscesses: CT evaluation. Clin Radiol 1999;54:792.

Damjanov I, Katz SM: Malakoplakia. Pathol Annu 1981;16:103–126.

Dasgupta P et al: Malakoplakia: von Hansemann's disease. BJU Int 1999;84:464.

Desmond N et al: Tuberculous epididymitis: A case report in an HIV seropositive male. Int J STD AIDS 1993;4:178.

Dixon L et al: *Chlamydia trachomatis* infection and non-gonococcal urethritis in homosexual and heterosexual men in Edinburgh. Int J STD AIDS 2002;13:425.

Dobyan DC et al: Renal malakoplakia reappraised. Am J Kidney Dis 1993;22:243.

Duncan JL: Differential effect of Tamm-Horsfall protein on adherence of *Escherichia coli* to transitional epithelial cells. J Infect Dis 1988;158:1379.

Edlin RS, Shapiro DJ, Hersh AL, et al: Antibiotic resistance patterns in outpatient pediatric urinary tract infections. J Urol 2013; 190:222.

Ernst E, Diekema D, BootsMiller B, et al: Are United States hospitals following national guidelines for the analysis and presentation of cumulative antimicrobial susceptibility data? Diagn Microbiol 2004;49(2):141–145.

Evans DJ Jr et al: Hemolysin and K antigens in relation to serotype and hemagglutination type of *Escherichia coli* isolated from extraintestinal infections. J Clin Microbiol 1981;13:171.

Evans JK et al: Incidence of symptomatic urinary tract infections in HIV seropositive patients and the use of cotrimoxazole as prophylaxis against *Pneumocystis carinii* pneumonia. Genitourin Med 1995;71:120.

Fair WR et al: Prostatic antibacterial factor: Identity and significance. Urology 1976;7:169.

Falagas ME et al: Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: A meta-analysis of randomized controlled trials. J Infect 2009;58(2):91–102.

Falahatkar S, Shahab E, Gholamjani Moghaddam K, Kazemnezhad E: Transurethral Intraprostatic Injection of Botulinum Toxin Type A for the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Results of a Prospective Pilot Double-Blind and Randomized Placebo-Controlled study. *BJU Int*. 2014 Oct 13.

Fihn SD: Clinical practice. Acute uncomplicated urinary tract infection in women. N Engl J Med. 349: 259-66, 2003.

Flores-Mireles A, Walker J, Caparon M, Hultgren S: Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nature Reviews Micro 2015 (13): 269-284.

Fontanilla T, Minaya J, Cortés C, Hernando CG, Arangüena RP, Arriaga J, et al: Acute complicated pyelonephritis: contrast-enhanced ultrasound. Abdom Radiol 2012;37(4):639.

Foxman B et al: Urinary tract infection among women aged 40 to 65: Behavioral and sexual risk factors. J Clin Epidemiol 2001;54:710.

Franz M, Horl W: Common errors in diagnosis and management of urinary tract infection: Clinical management. Nephrol Dial Transpl 1999;14(11):2754–2762.

Frederic N et al: Renal malakoplakia: Ultrasonic and computed appearances. J Belge Radiol 1981;64:361.

Freedman AL: Urologic diseases in North America Project: Trends in resource utilization for urinary tract infections in children. J Urol 2005;173(3):949–954.

Fudaba H, Ooba H, Abe T, Kamida T, Wakabayashi Y, Nagatomi H, et al: An adult case of cerebral malakoplakia successfully cured by treatment with antibiotics, bethanechol and ascorbic acid. J Neurol Sci 2014;342(1–2):192–196.

Garcia-Rodriguez JA, Munoz Bellido JL: Oral cephalosporins in uncomplicated urinary tract infections. Clin Microbiol Infect 2000;6:73.

Ghiro L et al: Retrospective study of children with acute pyelonephritis: Evaluation of bacterial etiology, antimicrobial susceptibility, drug management and imaging studies. Nephron 2002; 90:8.

Gilstrap LC III et al: Acute pyelonephritis in pregnancy: An anterospective study. Obstet Gynecol 1981;57:409.

Gilstrap LC III, Ramin SM: Urinary tract infections during pregnancy. Obstet Gynecol Clin North Am 2001;28:581.

Goodman M et al: Xanthogranulomatous pyelonephritis (XGP): A local disease with systemic manifestations. Report of 23 patients and review of the literature. Medicine (Baltimore) 1979; 58:171.

Griebling, TL: Urologic diseases in America project: Trends in resource use for urinary tract infections in men. J Urol 2005a;173(4):1288–1294.

Griebling TL: Urologic diseases in America project: Trends in resource use for urinary tract infections in women. J Urol 2005b;173(4):1281–1287.

Gugino L et al: Asymptomatic bacteriuria in human immunodeficiency (HIV)-infected women. Prim Care Update Ob Gyns 1998;5:146.

Gupta K et al: Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA 1999;281:736.

Gupta K, Hooton TM, Naber KG, et al: International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–e120.

Haraoka M, Hang L, Frendéus B, et al: Neutrophil recruitment and resistance to urinary tract infection. J Infect Dis 1999(180):1220–1229.

Hoberman A et al: Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics 1999;104:79.

Hoberman A, Charron M, Hickey R, et al: Imaging studies after a first febrile urinary tract infection in young children. New Engl J Med 2003;348:195–202.

Hoepelman AI et al: Bacteriuria in men infected with HIV-1 is related to their immune status (CD4+ cell count). AIDS 1992;6:179.

Hoepelman AI et al: Pathogenesis and management of bacterial urinary tract infections in adult patients with diabetes mellitus. Int J Antimicrob Agents 2003;22(Suppl 2):35–43.

Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, Stapleton AE, Stergachis A, Stamm WE: A prospective study of risk factors for symptomatic urinary tract infection in young women. New Engl J Med 1996;335:468–474.

Hovanec DL, Gorzynski EA: Coagglutination as an expedient for grouping *Escherichia coli* associated with urinary tract infections. J Clin Microbiol 1980;11:41.

Hsiao AL, Chen L, Baker MD: Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. Pediatrics 2006;117:1695.

Huang ES, Stafford RS: National patterns in the treatment of urinary tract infections in women by ambulatory care physicians. Arch Intern Med 2002;162:41.

Huang JJ, Tseng CC: Emphysematous pyelonephritis: Clinicoradiological classification, management, prognosis, and pathogenesis. Arch Intern Med 2000;160(6):797–805.

Hughes C et al: Hemolysin production as a virulence marker in symptomatic and asymptomatic urinary tract infections caused by *Escherichia coli*. Infect Immun 1983;39:546.

Hultgren SJ, Porter TN, Schaeffer AJ, Duncan JL: Role of type 1 pili and the effects of phase variation on lower urinary tract infections produced by Escherichia coli. Infect Immun 1985;50:370–377.

Iskandar SS et al: Lipid-laden foamy macrophages in renal cell carcinoma: Potential frozen section diagnostic pitfall. Pathol Res Pract 1993;189:549.

Jahnukainen T et al: Mechanisms of renal damage owing to infection. Pediatr Nephrol 2005;20(8):1043–1053.

Jeena PM et al: Bacteriuria in children attending a primary health care clinic: A prospective study of catheter stream urine samples. Ann Trop Paediatr 1996;16:293.

Jenkins RD et al: Review of urine microscopy for bacteriuria. JAMA 1986;255:3397.

Johnson L et al: Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. Am J Med 2008;121(10):876–884.

Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF: Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013;27(5):473–478.

Kahlmeter G: An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: The ECO.SENS Project. J Antimicrob Chemother 2003;51(1): 69–76.

Kallenius G et al: Occurrence of P-fimbriated *Escherichia coli* in urinary tract infections. Lancet 1981;2:1369.

Kanamaru S, Kurazono H, Terai A, Monden K, Kumon H, Mizunoe Y, et al: Increased biofilm formation in Escherichia coli isolated from acute prostatitis. Int J Antimicrob Agents 2006;28(Suppl 1): S21–S25.

Karaca Y et al: Co-trimoxazole and quinolone resistance in *Escherichia coli* isolated from urinary tract infections over the last 100 years. Int J Antimicrob Agents 2005;26(1):75–77.

Kawashima A, Sandler CM, Ernst RD, et al: Renal inflammatory disease: The current role of CT. Crit Rev Diagn Imaging 1997;38(5):369–415.

Kodner CM, Thomas Gupton EK: Recurrent urinary tract infections in women: Diagnosis and management. Am Fam Physician 2010;82:638–643.

Koff SA, Wagner TT, Jayanthi VR: The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol 1998;160:1019.

Koronakis V, Hughes C: Synthesis, maturation and export of the *E. coli* hemolysin. Med Microbiol Immunol (Berlin) 1996;185:65.

Kuo CC, Wu CF, Huang CC, et al: Xanthogranulomatous pyelonephritis: critical analysis of 30 patients. Int Urol Nephrol 2011;43(1):15–22.

Lau SM et al: Resistance rates to commonly used antimicrobials among pathogens of both bacteremic and non-bacteremic community-acquired urinary tract infection. J Microbiol Immunol Infect 2004;37(3):185–191.

Lawrenson RA, Logie JW: Antibiotic failure in the treatment of urinary tract infections in young women. J Antimicrob Chemother 2001;48:895.

Lebovitch S, Mydlo JH: HIV-AIDS: Urologic considerations. Urol Clin North Am 2008;35:59–68, vi.

Lee LK et al: The urologist and the patient infected with human immunodeficiency virus or with acquired immunodeficiency syndrome. BJU Int 2001;88:500.

Leport C et al: Bacterial prostatitis in patients infected with the human immunodeficiency virus. J Urol 1989;141:334.

Levtchenko EN et al: Role of Tc-99m DMSA scintigraphy in the diagnosis of culture negative pyelonephritis. Pediatr Nephrol 2001;16:503.

Likitnukul S et al: Epididymitis in children and adolescents: A 20-year retrospective study. Am J Dis Child 1987;141:41.

Lipsky BA: Prostatitis and urinary tract infection in men: What's new; what's true? Am J Med 1999;106:327.

Litwin MS, Saigal CS, Yano EM, Avila C, Geschwind SA, Hanley JM, Joyce GF, Madison R, Pace J, Polich SM, et al: Urologic diseases in America Project: Analytical methods and principal findings. J Urol 2005;173:933–937.

Locksmith G, Duff P: Infection, antibiotics, and preterm delivery. Semin Perinatol 2001;25:295.

Lomberg H et al: Influence of blood group on the availability of receptors for attachment of uropathogenic *Escherichia coli*. Infect Immun 1986;51:919.

Long JP Jr, Althausen AF: Malakoplakia: A 25-year experience with a review of the literature. J Urol 1989;141:1328.

Lorentz WB: Localization of urinary tract infection. Urol Clin North Am 1979;6:519.

Lorentzen M, Nielsen HO: Xanthogranulomatous pyelonephritis. Scand J Urol Nephrol 1980;14:193.

Lowe FC, Fagelman E: Cranberry juice and urinary tract infections: What is the evidence? Urology 2001;57:407.

Marcus N et al: Non-*Escherichia coli* versus *Escherichia coli* community-acquired urinary tract infections in children hospitalized in a tertiary center: Relative frequency, risk factors, antimicrobial resistance and outcome. Pediatr Infect Dis J 2005;24(7):581–585.

Marques LP et al: AIDS-associated renal tuberculosis. Nephron 1996;74:701.

Martinez JJ et al: Type 1 pilus-mediated bacterial invasion of bladder epithelial cells. Embo J 2000;19:2803.

Matsumoto T: Urinary tract infections in the elderly. Curr Urol Rep 2001;2:330.

McClure J et al: The ultrastructural features of malakoplakia. J Pathol 1981;134:13.

McGregor JA, French JI: Prevention of preterm birth. New Engl J Med 1998;339:1858; discussion 1860.

McKinnon PS, Davis SL: Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. Eur J Clin Microbiol Infect Dis. 2004;23:271–288.

Meares EM Jr: Acute and chronic prostatitis: Diagnosis and treatment. Infect Dis Clin North Am 1987;1:855.

Meares EM, Stamey TA: Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 1968;5:492.

Merimsky E, Feldman C: Perinephric abscess: Report of 19 cases. Int Surg 1981;66:79.

Miller LG, Tang AW: Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. Mayo Clinic Proc 2004;79(8):1048–1053; quiz 1053–1054.

Minassian MA et al: A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. Int J Antimicrob Agents 1998;10:39.

Mori R et al: Diagnostic performance of urine dipstick testing in children with suspected UTI: A systematic review of relationship with age and comparison with microscopy. Acta Paediatr 2010;99(4):581–584.

Nagy V, Kubej D: Acute bacterial prostatitis in humans: current microbiological spectrum, sensitivity to antibiotics and clinical findings. Urologia Internationalis 2012;89 (4):445–450.

Navas EL et al: Blood group antigen expression on vaginal cells and mucus in women with and without a history of urinary tract infections. J Urol 1994;152:345.

Nguyen HT et al: Trimethoprim in vitro antibacterial activity is not increased by adding sulfamethoxazole for pediatric *Escherichia coli* urinary tract infection. J Urol 2010;184(1):305–310.

Nickel JC: The Pre and Post Massage Test (PPMT): A simple screen for prostatitis. Tech Urol 1997;3:38.

Nickel JC: Antibiotics for bacterial prostatitis. J Urol 2000;163:1407.

Nickel JC: The management of acute pyelonephritis in adults. Can J Urol 2001;8:29.

Nickel JC et al: Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: A prospective multicenter clinical trial. J Urol 2001;165:1539.

Nickel JC, Moon T: Chronic bacterial prostatitis: An evolving clinical enigma. Urology 2005;66(1):2–8.

Nicolle LE: Urinary tract infection in geriatric and institutionalized patients. Curr Opin Urol 2002;12:51.

Nicolle LE: Urinary tract infection in diabetes. Curr Opin Infect Dis 2005;18(1):49–53.

Nicolle LE: Urinary catheter-associated infections. Infect Dis Clin North Am 2012;26:13–27.

Nicolle LE et al: The association of urinary tract infection with sexual intercourse. J Infect Dis 1982;146:579.

Nourse PJ, Cotton MF, Bates WD: Renal manifestations in children co-infected with HIV and disseminated tuberculosis. Pediatr Nephrol 2010;25:1759–1763.

O'Dea MJ et al: Non-specific granulomatous prostatitis. J Urol 1977;118:58.

Ofek I et al: Role of bacterial lectins in urinary tract infections: Molecular mechanisms for diversification of bacterial surface lectins. Adv Exp Med Biol 2000;485:183.

Ohkawa M et al: Non-specific eosinophilic granulomatous prostatitis responded favorably to an antimicrobial agent and a hydrocortisone. Int J Urol 2001;8:578.

Olvera-Posada D, García-Mora A, Culebro-García C, et al: Prognostic factors in emphysematous pyelonephritis. Actas Urol Esp 2012;19.

O'Mahony C: Treatment of non-specific urethritis should be two weeks, not 1. Sex Transm Infect 1999;75:449.

Ooi ST et al: Management of asymptomatic bacteriuria in patients with diabetes mellitus. Ann Pharmacother 2004;38(3):490–493.

Orskov I et al: O, K, H and fimbrial antigens in *Escherichia coli* serotypes associated with pyelonephritis and cystitis. Scand J Infect Dis Suppl 1982;33:18.

Osset J et al: Assessment of the capacity of *Lactobacillus* to inhibit the growth of uropathogens and block their adhesion to vaginal epithelial cells. J Infect Dis 2001;183:485.

Pak J et al: Tamm-Horsfall protein binds to type 1 fimbriated *Escherichia coli* and prevents *E. coli* from binding to uroplakin Ia and Ib receptors. J Biol Chem 2001;276:9924.

Pallet A, Hand K: Complicated urinary tract infections: Practical solutions for the treatment of multiresistant Gram-negative bacteria. J Antimicrobial Chemother 2010;65:iii25–iii33.

Parsons MA: Xanthogranulomatous gastritis: An entity or a secondary phenomenon? J Clin Pathol 1993;46:580.

Patel HD et al: Can urine dipstick testing for urinary tract infection at point of care reduce laboratory workload? J Clin Pathol 2005;6(1):18–31.

Petrack EM, Hafeez W: Testicular torsion versus epididymitis: A diagnostic challenge. Pediatr Emerg Care 1992;8:347.

Pfau A, Sacks TG: Effective postcoital quinolone prophylaxis of recurrent urinary tract infections in women. J Urol 1994;152:136.

Philbrick JT: Single dose for urinary tract infections. J Gen Intern Med 1986;1:207.

Raffi HS et al: Tamm-Horsfall protein acts as a general host-defense factor against bacterial cystitis. Am J Nephrol 2005;20(8):1043–1053.

Rajesh A, Jakanani G, Mayer N, et al: Computed tomography findings in xanthogranulomatous pyelonephritis. J Clin Imaging Sci 2011;1:45.

Raveenthiran V, Sam CJ: Epididymo-orchitis complicating anorectal malformations: Collective review of 41 cases. J Urol 2011; 186(4):1467–1472.

Raz R, Stamm WE: A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. New Engl J Med 1993;329:753.

Reid G, Burton J: Use of *Lactobacillus* to prevent infection by pathogenic bacteria. Microbes Infect 2002;4:319.

Roberts JA et al: Epitopes of the P-fimbrial adhesin of *E. coli* cause different urinary tract infections. J Urol 1997a;158:1610.

Roberts KB: Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011;128:595.

Roberts RO et al: A review of clinical and pathological prostatitis syndromes. Urology 1997b;49:809.

Ronald A: The etiology of urinary tract infection: Traditional and emerging pathogens. Am J Med 2002;113:14.

Rubin RH et al: An approach to evaluating antibacterial agents in the treatment of urinary tract infection. Clin Infect Dis 1992;14:S246; discussion S253.

Salo J, Uhari M, Helminen M, et al: Cranberry juice for the prevention of recurrences of urinary tract infections in children: A randomized placebo-controlled trial. Clin Infect Dis 2012;54:340.

Santucci RA, Krieger JN: Gentamicin for the practicing urologist: Review of efficacy, single daily dosing and "switch" therapy. J Urol 2000;163:1076.

Saperston K, Shapiro D, Hersh A, et al: A comparison of inpatient versus outpatient resistance patterns of pediatric urinary tract infection. J Urol 2014;191(5):1608–1613.

Schaeffer AJ: What do we know about the urinary tract infection-prone individual? J Infect Dis 2001;183:S66.

Schaeffer AJ: The expanding role of fluoroquinolones. Am J Med 2002;113:45.

Schaeffer AJ et al: Role of vaginal colonization in urinary tract infections (UTIs). Adv Exp Med Biol 1999;462:339.

Schaeffer AJ, Stuppy BA. Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. J Urol 1999;161:207–211.

Schappert SM: Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1997. Vital Health Stat 13 1999;i–iv:1–39.

Schieve LA et al: Urinary tract infection during pregnancy: Its association with maternal morbidity and perinatal outcome. Am J Public Health 1994;84:405.

Schlager TA: Urinary tract infections in children younger than 5 years of age: Epidemiology, diagnosis, treatment, outcomes and prevention. Paediatr Drugs 2001;3:219.

Scholes D et al: Risk factors associated with acute pyelonephritis in healthy women. Ann Intern Med 2005;142(1):20–27.

Schwenger EM, Tejani AM, Loewen PS: Probiotics for preventing urinary tract infections in adult and children. Cochrane Library. 2015.

Sepkowitz KA et al: Tuberculosis in the AIDS era. Clin Microbiol Rev 1995;8:180.

Shaikh N, Morone NE, Bost JE, et al: Prevalence of urinary tract infection in childhood: A meta-analysis. Pediatr Infect Dis 2008;27:302.

Shaikh N, Morone NE, Lopez J, et al: Does this child have a urinary tract infection? JAMA 2007;298:2895.

Shortliffe LM, McCue JD: Urinary tract infection at the age extremes: Pediatrics and geriatrics. Am J Med 2002;113:55.

Siegel JF et al: Minimally invasive treatment of renal abscess. J Urol 1996;155:52.

Singh-Grewal D, Macdessi J, Craig J: Circumcision for the prevention of urinary tract infection in boys: A systematic review of randomised trials and observational studies. Arch Dis Child 2005;90:853.

Sobel JD: Pathogenesis of urinary tract infection: Role of host defenses. Infect Dis Clin North Am 1997;11:531.

Sotto A et al: Risk factors for antibiotic-resistant *Escherichia coli* isolated from hospitalized patients with urinary tract infections: A prospective study. J Clin Microbiol 2001;39:438.

Srigley JR: Benign mimickers of prostatic adenocarcinoma. Mod Pathol 2004;17(3):328–348.

Staiman VS, Lowe FC: Prostatic disease in HIV-infected patients. AIDS Read 1995;5:165.

Stamm WE et al: Diagnosis of coliform infection in acutely dysuric women. New Engl J Med 1982;307:463.

Stamm WE, Norrby SR: Urinary tract infections: Disease panorama and challenges. J Infect Dis 2001;183:S1.

Stoller ML, Kogan BA: Sensitivity of 99m technetium-dimercapto-succinic acid for the diagnosis of chronic pyelonephritis: Clinical and theoretical considerations. J Urol 1986;135:977.

Subramanyam BR, Raghavendra BN, Bosniak MA, et al: Sonography of pyonephrosis: A prospective study. Am J Roentgenol 1983;140(5):991–993.

Svanborg C et al: Bacterial adherence and mucosal cytokine responses: Receptors and transmembrane signaling. Ann NY Acad Sci 1996;797:177.

Svanborg C et al: Host-parasite interaction in the urinary tract. J Infect Dis 1988;157:421.

Svenson SB et al: P-fimbriae of pyelonephritogenic *Escherichia coli:* Identification and chemical characterization of receptors. Infection 1983;11:61.

Tam VK et al: Renal parenchymal malakoplakia: A rare cause of ARF with a review of recent literature. Am J Kidney Dis 2003;41(6):E13–E17.

Tang HJ et al: Clinical characteristics of emphysematous pyelonephritis. J Microbiol Immunol Infect 2001;34:125.

Trauzzi SJ et al: Management of prostatic abscess in patients with human immunodeficiency syndrome. Urology 1994;43:629.

Vanbrabant P, Drieskens O, Blockmans D: 18-fluoro-deoxyglucose positron emission tomography may contribute to the diagnosis and follow-up of malakoplakia. Acta Clin Belg 2004 May-Jun. 59(3):138-42.

Vas W et al: Computed tomography and ultrasound appearance of bladder malakoplakia. J Comput Tomogr 1985;9:119.

Velciov S, Gluhovschi G, Trandafirescu V, Petrica L, Bozdog G, Gluhovschi C, et al: Specifics of the renal abscess in nephrology: Observations of a clinic from a county hospital in Western Romania. Rom J Intern Med 2011;49(1):59–66.

Wagenlehner FM et al: The role of antibiotics in chronic bacterial prostatitis. Int J Antimicrob Agents 2005:26(1):1–7.

Wagenlehner FM, Naber KG: Hospital-acquired urinary tract infections. J Hosp Infect 2000;46:171.

Waltzer WC: The urinary tract in pregnancy. J Urol 1981;125:271.

Wan YL et al: Predictors of outcome in emphysematous pyelonephritis. J Urol 1998;159:369.

Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE: Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999;29:745–758.

Weinberger M et al: Prostatic abscess in the antibiotic era. Rev Infect Dis 1988;10:239.

Wennerstrom M et al: Primary and acquired renal scarring in boys and girls with urinary tract infection. J Pediatr 2000;136:30.

Wettergren B et al: Epidemiology of bacteriuria during the first year of life. Acta Paediatr Scand 1985;74:925.

Whitfield C, Roberts IS: Structure, assembly and regulation of expression of capsules in *Escherichia coli*. Mol Microbiol 1999;31:1307.

Williams GJ et al: Absolute and relative accuracy of rapid urine tests for urinary tract infection in children: A meta-analysis. Lancet Infect Dis 2010;10(4):240–250.

Williams DH, Schaeffer AJ: Current concepts in urinary tract infections. Minerva Urol Nefrol 2004:56(1):15–31.

Wing DA: Pyelonephritis. Clin Obstet Gynecol 1998;41:515.

Wing DA et al: Outpatient treatment of acute pyelonephritis in pregnancy after 24 weeks. Obstet Gynecol 1999;94:683.

Wiswell TE, Roscelli JD: Corroborative evidence for the decreased incidence of urinary tract infections in circumcised male infants. Pediatrics 1986;78:96.

Wong ES, McKevitt M, Running K, et al. Management of recurrent urinary tract infections with patient-administered single-dose therapy. Ann Intern Med. 1985;102:302–307.

Wood EG, Dillon HC Jr: A prospective study of group B streptococcal bacteriuria in pregnancy. Am J Obstet Gynecol 1981;140:515.

Wyatt SH, Urban BA, Fishman EK: Spiral CT of the kidneys: Role in characterization of renal disease. Part I: Nonneoplastic disease. Crit Rev Diagn Imaging 1995;36(1):137.

Yu KJ, Wang TM, Chen HW, Wang HH. The dilemma in the diagnosis of acute scrotum: Clinical clues for differentiating between testicular torsion and epididymo-orchitis. Chang Gung Med J 2012;35(1):38–45.

Zimina OG, Rezun S, Armao D, Braga L, Semelka RC: Renal malacoplakia: Demonstration by MR imaging. Magn Reson Imaging 2002;20(8):611–614.

15

Specific Infections of the Genitourinary Tract

Emil A. Tanagho, MD; & Christopher J. Kane, MD, FACS

Specific infections are those caused by specific organisms, each of which causes a clinically unique disease with identifiable pathologic tissue reactions.

TUBERCULOSIS

The World Health Organization (WHO) estimates that 9.6 million new incident cases and 1.5 million deaths related to tuberculosis occurred in 2014. Nearly half of the global burden of tuberculosis occurs in China, India, and Indonesia. Tubercle bacilli may invade one or more (or even all) of the organs of the genitourinary tract and cause a chronic granulomatous infection that shows the same characteristics as tuberculosis in other organs. Urinary tuberculosis is a disease of young adults (60% of patients are between the ages of 20 and 40 years) and is more common in males than in females.

Etiology

The infecting organism is *Mycobacterium tuberculosis*, which reaches the genitourinary organs by the hematogenous route from the lungs. The primary site is seldom symptomatic or apparent.

The kidney and possibly the prostate are the primary sites of tuberculous infection in the genitourinary tract. All other genitourinary organs become involved by either ascent (prostate to bladder) or descent (kidney to bladder, prostate to epididymis). The testis may become involved by direct extension from epididymal infection.

Pathogenesis (Figure 15–1)

A. Kidney and Ureter

When a shower of tubercle bacilli hits the renal cortex, the organisms may be destroyed by normal tissue resistance. Evidence of this is commonly seen in autopsies of persons who have died of tuberculosis; only scars are found in the kidneys. However, if enough bacteria of sufficient virulence become lodged in the kidney and are not overcome, a clinical infection is established.

Tuberculosis of the kidney progresses slowly; it may take 15–20 years to destroy a kidney in a patient who has good resistance to the infection. As a rule, therefore, there is no renal pain and little or no clinical disturbance of any type until the lesion has involved the calyces or the pelvis, at which time, pus and organisms may be discharged into the urine. It is only at this stage that symptoms (of cystitis) are manifest. The infection then proceeds to the pelvic mucosa and the ureter, particularly its upper and vesical ends. This may lead to stricture and obstruction (hydronephrosis).

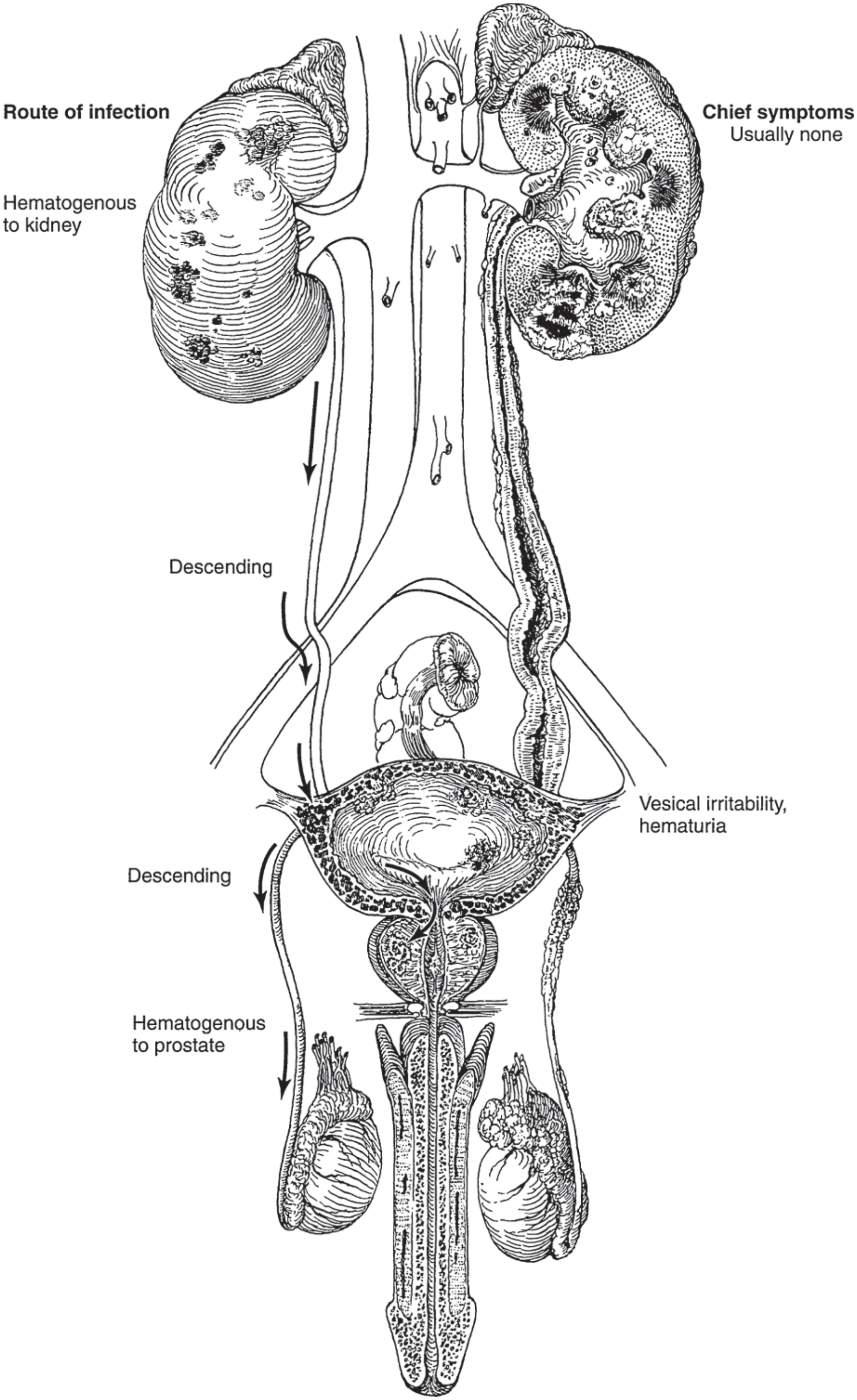
As the disease progresses, a caseous breakdown of tissue occurs until the entire kidney is replaced by cheesy material. Calcium may be laid down in the reparative process. The ureter undergoes fibrosis and tends to be shortened and therefore straightened. This change leads to a “golfhole” (gaping) ureteral orifice, typical of an incompetent valve.

B. Bladder

Vesical irritability develops as an early clinical manifestation of the disease as the bladder is bathed by infected material. Tubercles form later, usually in the region of the involved ureteral orifice, and finally coalesce and ulcerate. These ulcers may bleed. With severe involvement, the bladder becomes fibrosed and contracted; this leads to marked frequency. Ureteral reflux or stenosis and, therefore, hydronephrosis may develop. If contralateral renal involvement occurs later, it is probably a separate hematogenous infection.

C. Prostate and Seminal Vesicles

The passage of infected urine through the prostatic urethra ultimately leads to invasion of the prostate and one or both seminal vesicles. There is no local pain.



▲ **Figure 15–1.** Pathogenesis of tuberculosis of the urinary tract.

On occasion, the primary hematogenous lesion in the genitourinary tract is in the prostate. Prostatic infection can ascend to the bladder and descend to the epididymis.

D. Epididymis and Testis

Tuberculosis of the prostate can extend along the vas or through the perivasal lymphatics and affect the epididymis. Because this is a slow process, there is usually no pain. If the epididymal infection is extensive and an abscess forms, it may rupture through the scrotal skin, thus establishing a permanent sinus, or it may extend into the testicle.

Pathology

A. Kidney and Ureter

The gross appearance of the kidney with moderately advanced tuberculosis is often normal on its outer surface, although the kidney is usually surrounded by marked perinephritis. Usually, however, there is a soft, yellowish localized bulge. On section, the involved area is seen to be filled with cheesy material (caseation). Widespread destruction of parenchyma is evident. In otherwise normal tissue, small abscesses may be seen. The walls of the pelvis, calyces, and ureter may be thickened, and ulceration appears frequently in the region of the calyces at the point at which the abscess drains. Ureteral stenosis may be complete, causing **autonephrectomy**. Such a kidney is fibrosed and functionless. Under these circumstances, the bladder urine may be normal and symptoms absent.

Microscopically, the caseous material is seen as an amorphous mass. The surrounding parenchyma shows fibrosis with tissue destruction, small round cell and plasma cell infiltration, and epithelial and giant cells typical of tuberculosis. Acid-fast stains will usually demonstrate the organisms in the tissue. Similar changes can be demonstrated in the wall of the pelvis and ureter.

In both the kidney and ureter, calcification is common. It may be macroscopic or microscopic. Such a finding is strongly suggestive of tuberculosis but, of course, is also observed in bilharzial infection. Secondary renal stones occur in 10% of patients. In the most advanced stage of renal tuberculosis, the parenchyma may be completely replaced by caseous substance or fibrous tissue. Perinephric abscess may develop, but this is rare.

B. Bladder

In the early stages, the mucosa may be inflamed, but this is not a specific change. The bladder is quite resistant to actual invasion. Later, tubercles form and can be easily seen endoscopically as white or yellow raised nodules surrounded by a halo of hyperemia. With mural fibrosis and severe vesical contracture, reflux may occur.

Microscopically, the nodules are typical tubercles. These break down to form deep, ragged ulcers. At this stage, the bladder is quite irritable. With healing, fibrosis develops that involves the muscle wall.

C. Prostate and Seminal Vesicles

Grossly, the exterior surface of these organs may show nodules and areas of induration from fibrosis. Areas of necrosis are common. In rare cases, healing may end in calcification. Large calcifications in the prostate should suggest tuberculous involvement.

D. Spermatic Cord, Epididymis, and Testis

The vas deferens is often grossly involved; fusiform swellings represent tubercles that in chronic cases are characteristically described as beaded. The epididymis is enlarged and quite firm. It is usually separate from the testis, although occasionally it may adhere to it. Microscopically, the changes typical of tuberculosis are seen. Tubular degeneration may be marked. The testis is rarely involved except by direct extension of an abscess in the epididymis.

E. Female Genital Tract

Infections are usually carried by the bloodstream; rarely, they are the result of sexual contact with an infected male. The incidence of associated urinary and genital infection in women ranges from 1 to 10%. The uterine tubes may be affected. Other presentations include endarteritis, localized adnexal masses (usually bilateral), and tuberculous cervicitis, but granulomatous lesions of the vaginal canal and vulva are rare.

Clinical Findings

Tuberculosis of the genitourinary tract should be considered in the presence of any of the following situations: (l) chronic cystitis that refuses to respond to adequate therapy; (2) the finding of sterile pyuria; (3) gross or microscopic hematuria; (4) a nontender, enlarged epididymis with a beaded or thickened vas; (5) a chronic draining scrotal sinus; or (6) induration or nodulation of the prostate and thickening of one or both seminal vesicles (especially in a young man). A history of present or past tuberculosis elsewhere in the body should cause the physician to suspect tuberculosis in the genitourinary tract when signs or symptoms are present.

The diagnosis rests on the demonstration of tubercle bacilli in the urine by culture or positive polymerase chain reaction (PCR). The extent of the infection is determined by (1) the palpable findings in the epididymides, vasa deferentia, prostate, and seminal vesicles; (2) the renal and ureteral lesions as revealed by imaging; (3) involvement of the bladder as seen through the cystoscope; (4) the degree of renal damage as measured by loss of function; and (5) the presence of tubercle bacilli in one or both kidneys.

A. Symptoms

There is no classic clinical picture of renal tuberculosis. Most symptoms of this disease, even in the most advanced stage, are vesical in origin (cystitis). Vague generalized malaise, fatigability, low-grade but persistent fever, and night sweats are some of the nonspecific complaints. Even vesical irritability may be absent, in which case only proper collection and examination of the urine will afford the clue. Active tuberculosis elsewhere in the body is found in less than half of patients with genitourinary tuberculosis.

1. Kidney and ureter—Because of the slow progression of the disease, the affected kidney is usually completely asymptomatic. On occasion, however, there may be a dull ache in the flank. The passage of a blood clot, secondary calculi, or a mass of debris may cause renal and ureteral colic. Rarely, the presenting symptom may be a painless mass in the abdomen.

2. Bladder—The earliest symptoms of renal tuberculosis may arise from secondary vesical involvement. These include burning, frequency, and nocturia. Hematuria is occasionally found and is of either renal or vesical origin. At times, particularly in a late stage of the disease, the vesical irritability may become extreme. If ulceration occurs, suprapubic pain may be noted when the bladder becomes full.

3. Genital tract—Tuberculosis of the prostate and seminal vesicles usually causes no symptoms. The first clue to the presence of tuberculous infection of these organs is the onset of a tuberculous epididymitis.

Tuberculosis of the epididymis usually presents as a painless or only mildly painful swelling. An abscess may drain spontaneously through the scrotal wall. A chronic draining sinus should be regarded as tuberculous until proven otherwise. In rare cases, the onset is quite acute and may simulate an acute nonspecific epididymitis.

B. Signs

Evidence of extragenital tuberculosis may be found (lungs, bone, lymph nodes, tonsils, intestines).

1. Kidney—There is usually no enlargement or tenderness of the involved kidney.

2. External genitalia—A thickened, nontender, or only slightly tender epididymis may be discovered. The vas deferens often is thickened and beaded. A chronic draining sinus through the scrotal skin is almost pathognomonic of tuberculous epididymitis. In the more advanced stages, the epididymis cannot be differentiated from the testis on palpation. This may mean that the testis has been directly invaded by the epididymal abscess.

Hydrocele occasionally accompanies tuberculous epididymitis. The idiopathic hydrocele should be tapped so that underlying pathologic changes, if present, can be evaluated (epididymitis, testicular tumor). Involvement of the penis and urethra is rare.

3. Prostate and seminal vesicles—These organs may be normal to palpation. Ordinarily, however, the tuberculous prostate shows areas of induration, even nodulation. The involved seminal vesicle is usually indurated, enlarged, and fixed. If epididymitis is present, the ipsilateral seminal vesicle usually shows changes as well.

C. Laboratory Findings

Proper urinalysis affords the most important clue to the diagnosis of genitourinary tuberculosis.

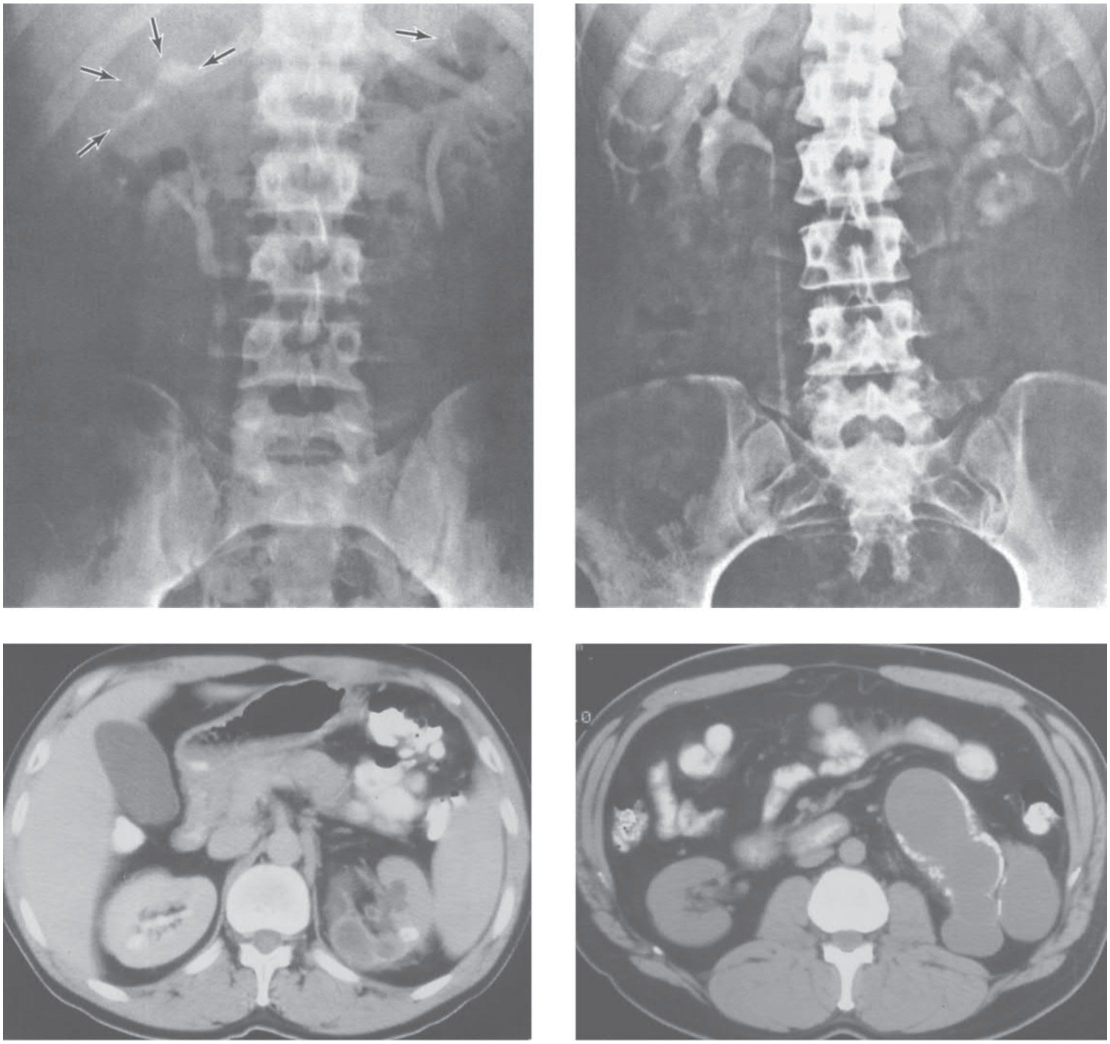
1. Persistent pyuria without organisms on culture means tuberculosis until proven otherwise. Acid-fast stains done on the concentrated sediment from a 24-hour specimen are positive in at least 60% of cases. However, this must be corroborated by a positive culture.
2. If clinical response to adequate treatment of bacterial infection fails and pyuria persists, tuberculosis must be ruled out by bacteriology and imaging.
3. Cultures for tubercle bacilli from the first morning urine are positive in a very high percentage of cases of tuberculous infection. If the cultures are positive, sensitivity tests should be ordered. In the face of strong presumptive evidence of tuberculosis, negative cultures should be repeated. Three to five first morning voided specimens are ideal.

If tuberculosis is suspected, the tuberculin test should be performed. A positive test, particularly in an adult, is hardly diagnostic, but a negative test in an otherwise healthy patient speaks against a diagnosis of tuberculosis.

D. X-Ray Findings (Figure 15–2)

A plain film of the abdomen may show enlargement of one kidney or obliteration of the renal and psoas shadows due to perinephric abscess. Punctate calcification in the renal parenchyma may be due to tuberculosis. Renal stones are found in 10% of cases. Calcification of the ureter may be noted, but this is rare (Figure 15–2).

Excretory urograms can be diagnostic if the lesion is moderately advanced. The typical changes include (1) a "moth-eaten" appearance of the involved ulcerated calyces; (2) obliteration of one or more calyces; (3) dilatation of the calyces due to ureteral stenosis from fibrosis; (4) abscess cavities that connect with calyces; (5) single or multiple ureteral strictures, with secondary dilatation, with shortening and therefore straightening of the ureter; and (6) the absence of function of the kidney due to complete ureteral occlusion and renal destruction (autonephrectomy). Ultrasound and computed tomography (CT) also show the calcifications, renal contractions and scars, and ureteral and calyceal strictures suggestive of genitourinary tuberculosis. Ultrasound has the advantage of low cost and low invasiveness. Contrast CT scan is highly sensitive for calcifications and the characteristic anatomic changes.



▲ **Figure 15–2.** Radiologic evidence of tuberculosis. ***Upper left:*** Excretory urogram showing "moth-eaten" calyces in upper renal poles. Calcifications in upper calyces; right upper ureter is straight and dilated. ***Upper right:*** Excretory urogram showing ulcerated and dilated calyces on the left. ***Lower left:*** Abdominal computed tomography (CT) with contrast showing left renal tuberculosis with calcification, poor parenchymal perfusion, and surrounding inflammation. ***Lower right:*** Noncontrast abdominal CT showing late effects of renal TB with calyceal dilation, loss of parenchyma, and urothelial calcifications. (CT images used with permission from Fergus Coakley, MD, UCSF Radiology.)

E. Cystoscopic Examination

Thorough cystoscopic study is indicated even when the offending organism has been found in the urine and excretory urograms show the typical renal lesion. This study clearly demonstrates the extent of the disease. Cystoscopy may reveal the typical tubercles or ulcers of tuberculosis. Biopsy can be done if necessary. Severe contracture of the bladder may be noted. A cystogram may reveal ureteral reflux.

▶ Differential Diagnosis

Chronic nonspecific cystitis or pyelonephritis may mimic tuberculosis perfectly, especially since 15–20% of cases of tuberculosis are secondarily invaded by pyogenic organisms. If nonspecific infections do not respond to adequate therapy, a search for tubercle bacilli should be undertaken. Painless epididymitis points to tuberculosis. Cystoscopic demonstration of tubercles and ulceration of the bladder wall means tuberculosis.

Acute or chronic nonspecific epididymitis may be confused with tuberculosis, since the onset of tuberculosis is occasionally quite painful. It is rare to have palpatory changes in the seminal vesicles with nonspecific epididymitis, but these are almost routine findings in tuberculosis of the epididymis. The presence of tubercle bacilli on a culture of the urine is diagnostic. On occasion, only the pathologist can make the diagnosis by microscopic study of the surgically removed epididymis.

Multiple small renal stones or nephrocalcinosis seen by x-ray may suggest the type of calcification seen in the tuberculous kidney. In renal tuberculosis, the calcium is in the parenchyma, although secondary stones are occasionally seen.

Necrotizing papillitis, which may involve all the calyces of one or both kidneys or, rarely, a solitary calyx, shows caliceal lesions (including calcifications) that simulate those of tuberculosis. Careful bacteriologic studies fail to demonstrate tubercle bacilli.

Medullary sponge kidneys may show small calcifications just distal to the calyces. The calyces are sharp, however, and no other stigmas of tuberculosis can be demonstrated.

In disseminated coccidioidomycosis, renal involvement may occur. The renal lesion resembles that of tuberculosis. Coccidioidal epididymitis may be confused with tuberculous involvement.

Urinary bilharziasis is a great mimic of tuberculosis. Both present with symptoms of cystitis and often hematuria. Vesical contraction, seen in both diseases, may lead to extreme frequency. Schistosomiasis must be suspected in endemic areas; the typical ova are found in the urine. Cystoscopic and urographic findings are definitive for making the diagnosis.

▶ Complications

A. Renal Tuberculosis

Perinephric abscess may cause an enlarging mass in the flank. A plain film of the abdomen shows obliteration of the renal and psoas shadows. Sonograms and CT scans may be more helpful. Renal stones may develop if secondary nonspecific infection is present. Uremia is the end stage if both kidneys are involved.

B. Ureteral Tuberculosis

Scarring with stricture formation is one of the typical lesions of tuberculosis and most commonly affects the juxtavesical portion of the ureter. This may cause progressive hydronephrosis. Complete ureteral obstruction may cause complete nonfunction of the kidney (autonephrectomy).

C. Vesical Tuberculosis

When severely damaged, the bladder wall becomes fibrosed and contracted. Stenosis of the ureters or reflux occurs, causing hydronephrotic atrophy.

D. Genital Tuberculosis

The ducts of the involved epididymis become occluded. If this is bilateral, sterility results. Abscesses of the epididymis may invade the testes and even involve the scrotal skin.

▶ Treatment

Genitourinary tuberculosis is extrapulmonary tuberculosis. The primary treatment is medical therapy. Surgical excision of an infected organ, when indicated, is merely an adjunct to overall therapy.

A. Nutrition and Anticholinergic Medications

Optimizing nutrition is important for the treatment of tuberculosis of the genitourinary tract. Anticholinergic medications may help with bladder irritability.

B. Treatment of Other Complications

Perinephric abscess usually occurs when the kidney is destroyed, but this is rare. The abscess must be drained, and nephrectomy should be done either then or later to prevent development of a chronic draining sinus. Prolonged antimicrobial therapy is indicated. If ureteral stricture develops on the involved side, ureteral dilatations offer a better than 50% chance of cure. The severely involved bladder may cause incompetence of the ureterovesical junction on the uninvolved side. Ureteroneocystostomy cannot be done in such a bladder; some form of urinary diversion may be required. For this reason, serial imaging and assessments of renal function are necessary, even when the treatment is medical.

CANDIDIASIS

Candida albicans is a yeastlike fungus that is a normal inhabitant of the respiratory and gastrointestinal tracts and the vagina. The intensive use of potent modern antibiotics is apt to disturb the normal balance between normal and abnormal organisms, thus allowing fungi such as *Candida* to overwhelm an otherwise healthy organ. The bladder and, to a lesser extent, the kidneys have proved vulnerable; candidemia has been observed (Table 15–1).

The patient may present with vesical irritability or symptoms and signs of pyelonephritis. Fungus balls may be passed spontaneously. The diagnosis is made by observing mycelial

Table 15–1. Risk factors for fungal UTI.

Indwelling catheters
Antimicrobials
Diabetes mellitus
Impaired host immunity including malignancy, steroids, malnutrition
Genitourinary tract abnormalities

UTI, urinary tract infection.

or yeast forms of the fungus microscopically in a properly collected urine specimen. The diagnosis may be confirmed by culture. Treatment of candiduria in asymptomatic catheterized patients is typically not of utility. Oral fluconazole may transiently clear funguria, but it typically recurs promptly and may recur with resistant candida species. Vesical candidiasis usually responds to alkalinization of the urine with sodium bicarbonate. A urinary pH of 7.5 is desired; the dose is regulated by the patient, who checks the urine with indicator paper. Candiduria should be treated in symptomatic patients, patients with neutropenia, renal transplant patients, and patients who will undergo urologic procedures.

Removing or changing urologic catheters, stent, and tubes may be beneficial. Treatment with fluconazole (200 mg/day for 7–14 days) or with amphotericin B deoxycholate at widely ranging doses (0.3–1.0 mg/kg per day for 1–7 days) has been successful. In the absence of renal insufficiency, oral flucytosine (25 mg/kg qid [4 times per day]) may be valuable for eradicating candiduria in patients with urologic infection due to non-*albicans* species of *Candida*.

ACTINOMYCOSIS

Actinomycosis is a chronic granulomatous disease in which fibrosis tends to become marked and spontaneous fistulas are the rule. On rare occasions, the disease involves the kidney, bladder, or testis by hematogenous invasion from a primary site of infection. The skin of the penis or scrotum may become involved through a local abrasion. The bladder may also become diseased by direct extension from the appendix, bowel, or oviduct.

Etiology

Actinomyces israelii is the causative organism.

Clinical Findings

There is nothing specifically pathognomonic about the symptoms or signs in actinomycosis. Pelvic involvement can be confused with malignancy. The microscopic demonstration of the organisms, which are visible as yellow bodies called **sulfur granules**, makes the diagnosis. If persistently sought, these may be found in the discharge from sinuses or in the urine. Definitive diagnosis is established by culture.

Urographically, the lesion in the kidney may resemble tuberculosis (eroded calyces) or tumor (space-occupying lesion).

Treatment

Penicillin G is the drug of choice. The dosage is 10–20 million U/day parenterally for 4–6 weeks, followed by penicillin V orally for a prolonged period. If secondary infection is suspected, a sulfonamide is added; streptomycin is also efficacious. Broad-spectrum antibiotics are indicated only if the organism is resistant to penicillin. Surgical drainage of the abscess or, better, removal of the involved organ is usually indicated.

Prognosis

Removal of the involved organ (eg, kidney or testis) may be promptly curative. Drainage of a granulomatous abscess may cause the development of a chronic draining sinus. Chemotherapy is helpful.

SCHISTOSOMIASIS (BILHARZIASIS)

Schistosomiasis, caused by a blood fluke, is a disease of warm climates. In its three forms, it affects about 350 million people. *Schistosoma mansoni* is widely distributed in Africa, South and Central America, Pakistan, and India; *Schistosoma japonicum* is found in the Far East; and *Schistosoma haematobium* (*Bilharzia haematobium*) is limited to Africa (especially along its northern coast), Saudi Arabia, Israel, Jordan, Lebanon, and Syria.

Schistosomiasis is on the increase in endemic areas because of the construction of modern irrigation systems that provide favorable conditions for the intermediate host, a freshwater snail. This disease principally affects the urogenital system, especially the bladder, ureters, seminal vesicles, and, to a lesser extent, the male urethra, and prostate gland. Because of emigration of people from endemic areas, the disease is being seen with increasing frequency in both Europe and the United States. Infection with *S. mansoni* and *S. japonicum* mainly involves the colon.

Etiology

Humans are infected when they come in contact with larva-infested water in canals, ditches, or irrigation fields during swimming, bathing, or farming procedures. Fork-tailed larvae, the cercariae, lose their tails as they penetrate deep under the skin. They are then termed **schistosomules**. They cause allergic skin reactions that are more intense in people infected for the first time. These schistosomules enter the general circulation through the lymphatics and the peripheral veins and reach the lungs. If the infection is massive, they may cause pneumonitis. They pass through the pulmonary circulation, to the left side of the heart, and to the general circulation. The worms that reach the vesicoprostatic plexus of veins survive and mature, whereas those that go to other areas die.

Pathogenesis

The adult *S. haematobium* worm, a digenetic trematode, lives in the prostatovesical plexus of veins. The male is about 10 × 1 mm in size; is folded on itself; and carries the long, slim, 20 × 0.25-mm female in its “schist,” or gynecophoric canal. In the smallest peripheral venules, the female leaves the male and partially penetrates the venule to lay her eggs in the subepithelial layer of the affected viscus, usually in the form of clusters that form tubercles. The ova are seen only rarely within the venules; they are almost always in the subepithelial or interstitial tissues. The female returns to the male, which carries her to other areas to repeat the process.

The living ova, by a process of histolysis and helped by contraction of the detrusor muscle, penetrate the overlying urothelium, pass into the cavity of the bladder, and are extruded with the urine. If these ova reach freshwater, they hatch, and the contained larvae—ciliated miracidia—find a specific freshwater snail that they penetrate. There, they form sporocysts that ultimately form the cercariae, which leave the snail hosts and pass into freshwater to repeat their lifecycle in the human host.

Pathology

The fresh ova excite little tissue reaction when they leave the human host promptly through the urothelium. The contents of the ova trapped in the tissues and the death of the organisms cause a severe local reaction, with infiltration of round cells, monocytes, eosinophils, and giant cells that form tubercles, nodules, and polyps. These are later replaced by fibrous tissue that causes contraction of different parts of the bladder and strictures of the ureter. Fibrosis and massive deposits of eggs in subepithelial tissues interfere with the blood supply of the area and cause chronic bilharzial ulcerations. Epithelial metaplasia is common, and squamous cell carcinoma is a frequent sequela. Secondary infection of the urinary tract is a common complication and is difficult to overcome. The trapped dead ova become impregnated with calcium salts and form sheets of subepithelial calcified layers in the ureter, bladder, and seminal vesicles.

Clinical Findings

A. Symptoms

Penetration of the skin by the cercariae causes allergic reactions, with cutaneous hyperemia and itching that are more intense in people infected for the first time. During the stage of generalization or invasion, the patient complains of symptoms such as malaise, fatigue and lassitude, low-grade fever, excessive sweating, headache, and backache. When the ova are laid in the bladder wall and begin to be extruded, the patient complains of terminal, slightly painful hematuria that is occasionally profuse. This may remain the only complaint for a long time until complications set in, when vesical symptoms become exaggerated and progressive. Increasing frequency, suprapubic and back pain, urethralgia, profuse hematuria, pyuria, and necroturia (dead cells in urine) are likely to occur, with secondary infection, ulceration, or malignancy. Renal pain may be due to ureteral stricture, vesicoureteral reflux, or secondary stones obstructing the ureter. Fever, rigor, toxemia, and uremia are manifestations of renal involvement.

B. Signs

In early uncomplicated cases, there are essentially no clinical findings. Later, a fibrosed, pitted, bilharzial glans penis; a urethral stricture or fistula; or a perineal fibrous mass may be found. A suprapubic bladder mass or a renal swelling may be felt abdominally. Rectal examination may reveal a fibrosed prostate, an enlarged seminal vesicle, or a thickened bladder base.

C. Laboratory Findings

Urinalysis usually reveals the terminus-spined dead or living ova, blood and pus cells, and bacteria. Malignant squamous cells may be seen. The complete blood count usually shows leukocytosis with eosinophilia and hypochromic normocytic anemia. Serum creatinine and blood urea nitrogen measurements may demonstrate some degree of renal impairment.

A variety of immunologic methods have been used to confirm the diagnosis of schistosomiasis. Positive immunologic tests indicate previous exposure but not whether schistosomiasis is currently present. The cercariae, schistosomules, adult worms, and eggs are all potentially antigenic. Adult worms, however, acquire host antigen on their integument that circumvents the immunologic forces of the host. Antibody production may be manifested as hypergammaglobulinemia.

D. X-Ray Findings

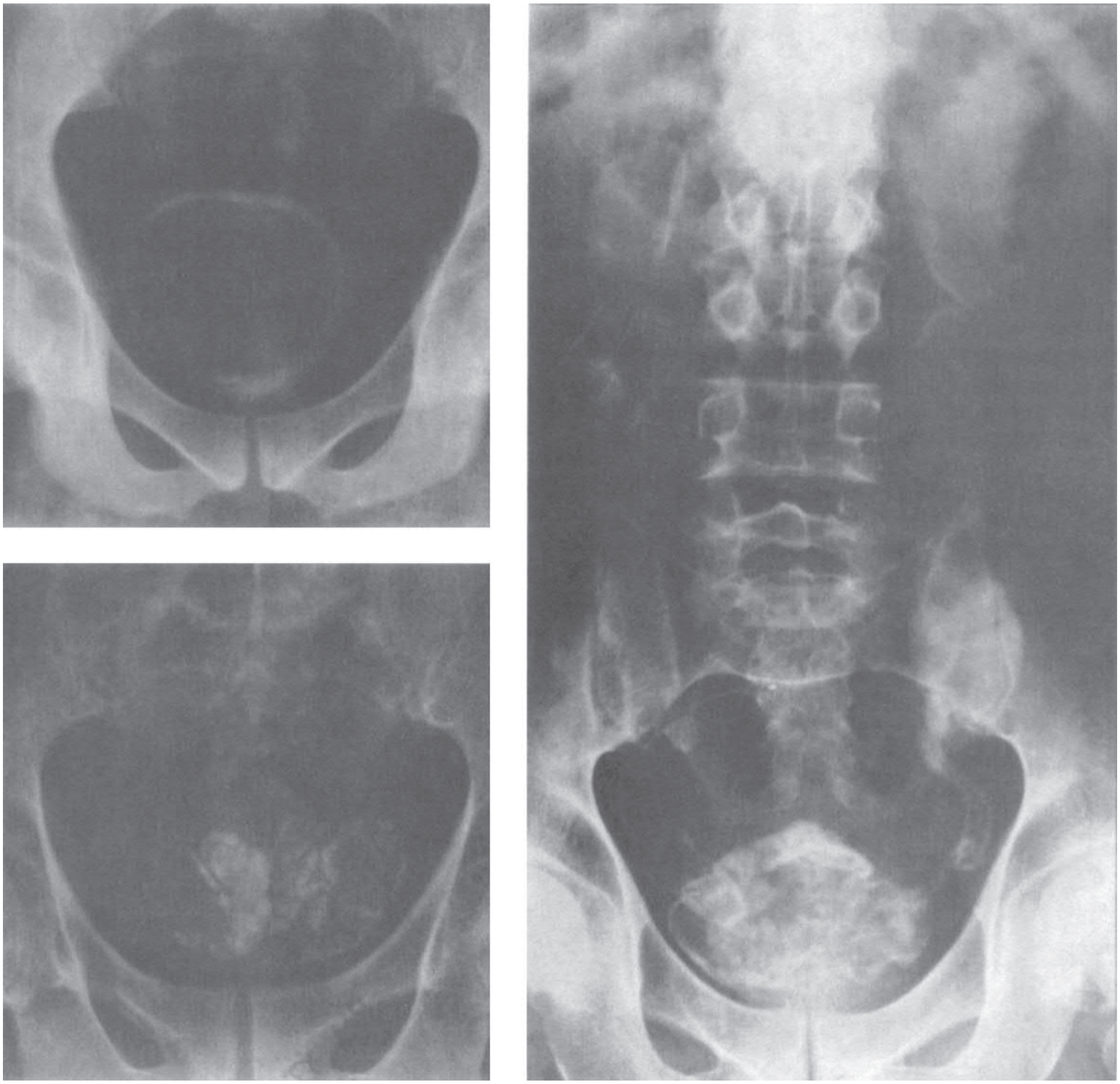
A plain film of the abdomen may show areas of grayness in the flank (enlarged hydronephrotic kidney) or in the bladder area (large tumor). Opacifications (stones) may be noted in the kidney, ureter, or bladder. Linear calcification may be seen in the ureteral and bladder walls (Figure 15–3). Punctate calcification of the ureter (ureteritis calcinosa) and a honeycombed calcification of the seminal vesicle may be obvious (Figure 15–3).

Excretory urograms may show either normal or diminished renal function and varying degrees of dilatation of the upper urinary tracts (Figure 15–4). These changes include hydronephrosis, dilated and tortuous ureters, ureteral strictures, or a small contracted bladder having a capacity of only a few milliliters. Gross irregular defects of the bladder wall may represent cancer (Figure 15–4). Abdominal and pelvic CT is replacing excretory urography as the initial imaging of choice in many centers.

Retrograde urethrography may reveal a bilharzial urethral stricture. Cystograms often reveal vesicoureteral reflux, particularly if the bladder is contracted.

E. Cystoscopic Examination

Cystoscopy may show fresh conglomerate, grayish tubercles surrounded by a halo of hyperemia, old calcified yellowish tubercles, sandy patches of mucous membrane, and a lusterless ground-glass mucosa that lacks the normal vascular pattern. Other obvious lesions include bilharzial polyps; chronic ulcers on the dome that bleed when the bladder is deflated (weeping ulcers); vesical stones; malignant lesions; stenosed or patulous ureteric orifices; and a distorted, asymmetric trigone. All are signs of schistosomal infestation.



▲ **Figure 15–3.** Schistosomiasis. Plain films. ***Upper left:*** Extensive calcification in the wall of a contracted bladder. ***Right:*** Extensive calcification of the bladder and both ureters up to the renal pelvis. The ureters are dilated and tortuous. ***Lower left:*** Extensive calcification of seminal vesicles and ampullae of vasa.

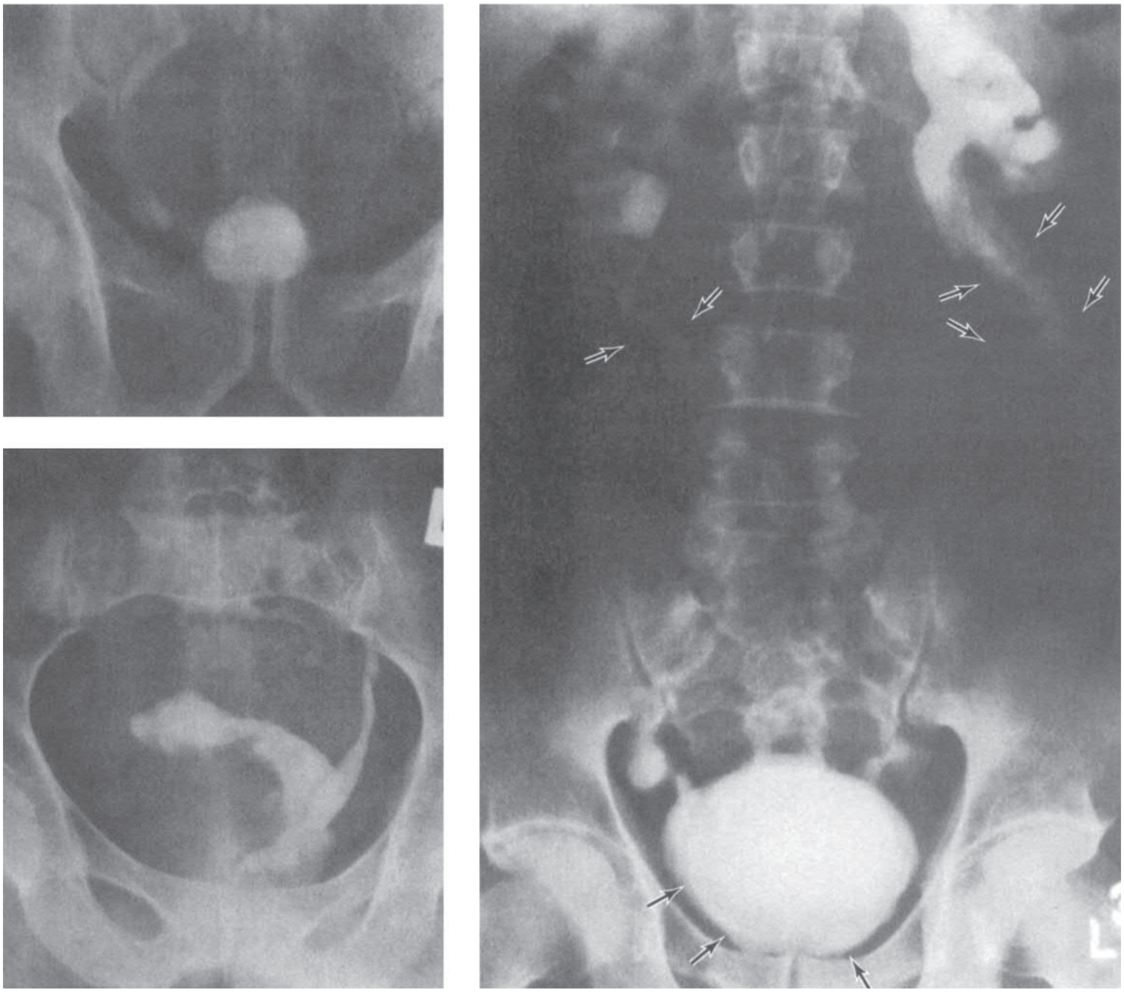
▶ Differential Diagnosis

Bilharzial cystitis is unmistakable in endemic areas. The presence of schistosomal ova in the urine, together with radiographic and cystoscopic findings, usually confirms the diagnosis. Nonspecific cystitis usually responds to medical treatment unless there is a complicating factor. Tuberculous cystitis may mimic bilharzial cystitis; the detection of tubercle bacilli, together with the radiographic picture, is confirmatory, but tuberculosis may occur in a bilharzial bladder. Squamous cell tumors of the bladder are common. They are observed as early as the second or third decade of life and are much more common in men than in women.

▶ Treatment

A. Medical Measures

Praziquantel, metrifonate, and oxamniquine are the drugs of choice in treating schistosomiasis. These drugs do not



▲ **Figure 15–4.** Schistosomiasis. ***Upper left:*** Excretory urogram showing markedly contracted bladder. Lower right ureter dilated probably secondary to vesicoureteral reflux. ***Right:*** Excretory urogram at 2 hours showing a fairly normal right kidney. The upper ureter is distorted. *Arrows* point to calcified wall. The lower ureter is quite abnormal. The calyces and pelvis of the left kidney are dilated, but the kidney shows atrophy secondary to nonspecific infection. The upper ureter is dilated and displaced by elongation due to obstruction. *Arrows* show calcification. Linear calcification can be seen in the periphery of the lower half of the bladder wall (*arrows*). ***Lower left:*** Nodular squamous cell carcinoma of the bladder. Dilated left lower ureter probably secondary to obstruction by tumor. Nonvisualization of the right ureter caused by complete occlusion.

have the serious side effects associated with the older drugs (eg, antimonials).

1. Praziquantel—This is unique in that it is effective against all human schistosome species. It is given orally and is effective in adults and children. Patients in the hepatosplenic stage of advanced schistosomiasis tolerate the drug well. The recommended dosage for all forms of schistosomiasis is 20 mg/kg 3 times (tid) in 1 day only.

2. Metrifonate—This is also a highly effective oral drug. It is the drug of choice for treatment of *S. haematobium* infections but is not effective against *S. mansoni* or *S. japonicum*. For treatment of *S. haematobium* infections, the dosage is 7.5–10 mg/kg (maximum 600 mg) once and then repeated twice at 2-week intervals.

3. Oxamniquine—This is a highly effective oral drug and is the drug of choice for treatment of *S. mansoni* infections. It is safe and effective in advanced disease. It is not effective in *S. haematobium* or *S. japonicum* infections. The dosage is 12–15 mg/kg given once; for children <30 kg, 20 mg/kg is given in two divided doses in 1 day, with an interval of 2–8 hours between doses. Cure rates are 70–95%.

4. Niridazole—This is a nitrothiazole derivative and is effective in treating *S. mansoni* and *S. haematobium* infections. It may be tried against *S. japonicum* infections. It is given orally and should be administered only under close medical supervision. The dosage is 25 mg/kg (maximum, 1.5 g) daily in two divided doses for 7 days. Side effects may include nausea, vomiting, anorexia, headache, T-wave depression, and temporary suppression of spermatogenesis.

B. General Measures

Antibiotics or urinary antiseptics are needed to overcome or control secondary infection. Supportive treatment in the form of iron, vitamins, and a high-calorie diet is indicated in selected cases.

C. Complications

Treatment of the complications of schistosomiasis of the genitourinary tract makes demands on the skill of the physician. Juxtavesical ureteral strictures require resection of the stenotic segment with ureteroneocystostomy. If the ureter is not long enough to reimplant, a tube of bladder may be fashioned, turned cephalad, and anastomosed to the ureter. Vesicoureteral reflux requires a suitable surgical repair. A contracted bladder neck may need transurethral anterior commissurotomy or a suprapubic Y-V plasty.

A chronic "weeping" bilharzial bladder ulcer necessitates partial cystectomy. The contracted bladder is treated by enterocystoplasty (placing a segment of bowel as a patch on the bladder). This procedure, which significantly increases vesical capacity, is remarkably effective in lessening the severity of symptoms associated with contracted bladder. Preoperative vesicoureteral reflux may disappear.

The most dreaded complication, squamous cell carcinoma, requires radical cystectomy with urinary diversion if the lesion is deemed operable. Unfortunately, late diagnosis is common.

Prognosis

With early diagnosis and treatment, mild and early cases of schistosomiasis can be effectively treated usually without complications. On the other hand, massive repeated infections undermine the function of the urinary tract to such an extent that patients are chronically ill and may have shortened lifespans.

In many endemic areas, attempts have been made to control the disease by mass treatment of patients, proper education, mechanization of agriculture, and various methods of eradication or control of the snail population. All these efforts have failed to be fully effective.

FILARIASIS

Filariasis is endemic in the countries bordering the Mediterranean, in south China and Japan, in the West Indies, and in the South Pacific islands, particularly Samoa. Limited infection, as seen in American soldiers during World War II, gives an entirely different clinical picture from that seen in the frequent reinfections usually encountered among the native population.

Etiology

Wuchereria bancrofti is a threadlike nematode about 0.5 cm or more in length that lives in the human lymphatics. In the lymphatics, the female gives off microfilariae, which are found in the peripheral blood, particularly at night. The intermediate host (usually a mosquito) bites an infected person and becomes infested with microfilariae, which develop into larvae. These are, in turn, transferred to another human, in whom they reach maturity. Mating occurs, and microfilariae are again produced. *Brugia malayi*, a nematode that causes filariasis in Southeast Asia and adjacent Pacific islands, acts in a similar fashion.

Pathogenesis and Pathology

The adult nematode in the human host invades and obstructs the lymphatics; this leads to lymphangitis and lymphadenitis. In longstanding cases, the lymphatic vessels become thickened and fibrous; there is a marked reticuloendothelial reaction.

Clinical Findings

A. Symptoms

In mild cases (few exposures), the patient suffers recurrent lymphadenitis and lymphangitis with fever and malaise. Not infrequently, inflammation of the epididymis, testis, scrotum, and spermatic cord occurs. These structures then become edematous, boggy, and, at times, tender. Hydrocele is common. In advanced cases (many exposures), obstruction of major lymph channels may cause chyluria and elephantiasis.

B. Signs

Varying degrees of painless elephantiasis of the scrotum and extremities develop as obstruction to lymphatics progresses. Lymphadenopathy is common.

C. Laboratory Findings

Chylous urine may appear normal if minimal amounts of fat are present, but in an advanced case or following a fatty meal, it is milky. On standing, the urine forms layers: the top layer is fatty, the middle layer is pinkish, and the lower layer is clear. In the presence of chyluria, large amounts of protein are to be expected. Hypoproteinemia is found, and the albumin:globulin ratio is reversed. Both white blood cells (leukocytes) and red blood cells (erythrocytes) are found.

Marked eosinophilia is the rule in the early stages. Microfilariae may be demonstrated in the blood, which should be drawn at night. The adult worm may be found by biopsy. When filariae cannot be found, an indirect hemagglutination titer of $^1/_{128}$ and a bentonite flocculation titer of $^1/_5$ in combination are considered diagnostic.

D. Cystoscopy

Following a fatty meal, endoscopy to observe the efflux of milky urine from the ureteral orifices may differentiate between unilateral and bilateral cases.

E. X-Ray Findings

Retrograde urography and lymphangiography may reveal the renolymphatic connections in patients with chyluria.

Prevention

In endemic areas, mosquito abatement programs must be intensively pursued.

Treatment

A. Specific Measures

Diethylcarbamazine administered 0.5–2 g/kg for 3 weeks or albendazole 400 mg orally twice daily are the treatments of choice. Antibiotics may be necessary to control secondary infection.

B. General Measures

Prompt removal of recently infected patients from the endemic area almost always results in regression of the symptoms and signs in early cases.

C. Surgical Measures

Elephantiasis of the external genitalia may require surgical excision.

D. Treatment of Chyluria

Mild cases require no therapy. Spontaneous cure occurs in 50% of cases. If nutrition is impaired, the lymphatic channels may be sealed off by irrigating the renal pelvis with 2% silver nitrate solution. Should this fail, renal decapsulation and resection of the renal lymphatics should be performed. This can now be performed laparoscopically with diminished morbidity.

Prognosis

If exposure has been limited, resolution of the disease is spontaneous, and the prognosis is excellent. Frequent reinfection may lead to elephantiasis of the scrotum or chyluria.

ECHINOCOCCOSIS (HYDATID DISEASE)

Involvement of the urogenital organs by hydatid disease is relatively rare in the United States. It is common in Australia, New Zealand, South America, Africa, Asia, the Middle East, and Europe. Livestock are the intermediate hosts. Canines, especially dogs, are the final hosts.

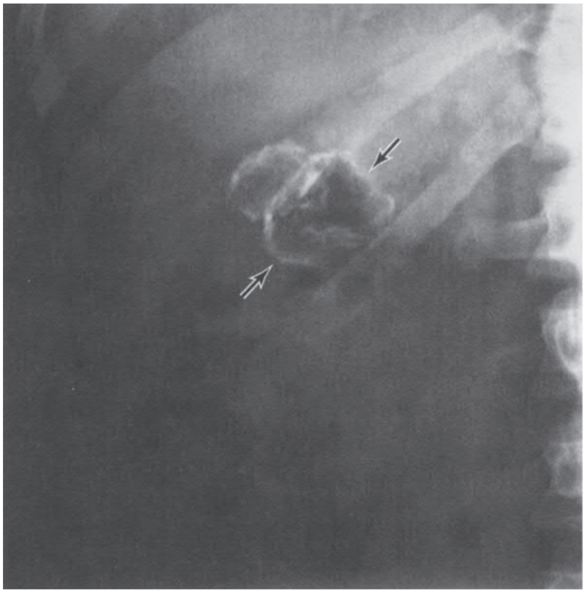
Etiology

The adult tapeworm (*Echinococcus granulosus*) inhabits the intestinal tracts of carnivorous animals. Its eggs pass out with the feces and may be ingested by such animals as sheep, cattle, pigs, and occasionally humans. Larvae from these eggs pass through the intestinal wall of the various intermediate hosts and are disseminated throughout the body. In humans, the liver is principally involved, but about 3% of infected humans develop echinococcosis of the kidney.

If a cyst of the liver should rupture into the peritoneal cavity, the scoleces (tapeworm heads) may directly invade the retrovesical tissues, thus leading to the development of cysts in this area.

Clinical Findings

If renal hydatid disease is closed (not communicating with the pelvis), there may be no symptoms until a mass is found. With communicating disease, there may be symptoms of cystitis, and renal colic may occur as cysts are passed from the kidney. X-ray films may show calcification in the wall of the cyst (Figure 15–5),



▲ **Figure 15–5.** Hydatid disease, right kidney. Plain film showing two calcified hydatid cysts.

and urograms often reveal changes typical of a space-occupying lesion. The cystic nature of the lesion may be demonstrated on sonograms and CT scans. Calcification in the cyst wall may be noted. Scintillation scanning or angiography can also suggest the presence of a cyst. Serologic tests that should be done include immunoelectrophoresis and indirect hemagglutination. The Casoni intracutaneous procedure is unreliable when teasting for nonliver disease and is no longer used.

Retroperitoneal (perivesical) cysts may cause symptoms of cystitis, or acute urinary retention may develop secondary to pressure. The presence of a suprapubic mass may be the only finding. It may rupture into the bladder and cause hydatiduria, which establishes the diagnosis.

Treatment

Nephrectomy is generally the treatment of choice for renal hydatid disease. Medical treatment includes albendazole 400 mg twice daily or praziquantel 40 mg/kg daily (before surgery). Aspiration of the cyst is unwise; leakage or rupture may occur. Retroperitoneal cysts are best treated by marsupialization and curettage.

Prognosis

Echinococcosis of the kidney usually has a good prognosis. The problem presented by perivesical cysts is more troublesome. After surgical intervention, drainage may be prolonged. It must be remembered, too, that involvement of other organs, especially the liver, is usually present.

BIBLIOGRAPHY

Tuberculosis

Carl P, Stark L: Indications for surgical management of genitourinary tuberculosis. World J Surg 1997;21:505.

Cek M et al: EAU guidelines for the management of genitourinary tuberculosis. Eur Urol 2005;48(3):353.

Chuang FR et al: Extrapulmonary tuberculosis in chronic hemodialysis patients. Ren Fail 2003;25:739.

Hemal AK et al: Polymerase chain reaction in clinically suspected genitourinary tuberculosis: Comparison with intravenous urography, bladder biopsy, and urine acid fast bacilli culture. Urology 2000;56:570.

Jung YY et al: Genitourinary tuberculosis: Comprehensive cross-sectional imaging. Am J Roentgenol 2005;184(1):143.

Kulchavenya E, Kholtobin D: Diseases masking and delaying the diagnosis of urogenital tuberculosis. Ther Adv Urol 2015;7(6): 331–338.

Lenk S, Schroeder J: Genitourinary tuberculosis. Curr Opin Urol 2001;11:93.

Matos MJ et al: Genitourinary tuberculosis. Eur J Radiol 2005;55 (2):181.

Queipo JA et al: Mycobacterial infection in a series of 1261 renal transplant recipients. Clin Microbiol Infect 2003;9:518.

Skoutelis A et al: Serious complications of tuberculous epididymitis. Infection 2000;28:193.

Sulis G et al: Recent developments in the diagnosis and management of tuberculosis. SNPJ Prim Care Respir Med 2016;26:16078.

Valentini AL et al: Diagnostic imaging of genitourinary tuberculosis. Rays 1998;23:126.

Yuan J. Genitourinary presentation of tuberculosis. Rev Urol 2015; 17(2):102–105 (doi: 10.3909/riu0679).

Candidiasis

Kauffman CA et al: Candida urinary tract infections--diagnosis. Clin Infect Dis. 2011;52(Suppl 6):S452–S4526.

Pappas PG et al: Guidelines for treatment of Candidiasis. Clin Infect Dis 2004;38:165–167.

Rodgers CA, Beardall AJ: Recurrent vulvovaginal candidiasis: Why does it occur? Int J STD AIDS 1999;10:435.

Sobel JD et al: Candiduria: A randomized, double-blind study of treatment with fluconazole and placebo. Clin Infect Dis 2000; 30:19–24.

Thomas L, Tracy CR: Treatment of fungal urinary tract infection. Urol Clin North Am 2015;42(4):473–483.

Wise GJ et al: Fungal infections of the genitourinary system: Manifestations, diagnosis, and treatment. Urol Clin North Am 1999;26:701.

Woolley PD, Higgins SP: Comparison of clotrimazole, fluconazole and itraconazole in vaginal candidiasis. Br J Clin Pract 1995;49:65.

Schistosomosias (Bilharziasis)

Jani AN et al: Disseminated actinomycosis presenting as a testicular mass: A case report. J Urol 1990;143:1012.

Lee YC et al: Computed tomography guided core needle biopsy diagnosis of pelvic actinomycosis. Gynecol Oncol 2000;79:318.

Lippes J: Pelvic actinomycosis: A review and preliminary look at prevalence. Am J Obstet Gynecol 1999;180(Pt 1):265.

Valour F et al: Actinomycosis: etiology, clinical features, diagnosis, treatment, and management Infect Drug Resist 2014;7:183–197.

Schistosomiasis (Bilharziasis)

Badawi AF et al: Role of schistosomiasis in human bladder cancer: Evidence of association, aetiological factors, and basic mechanisms of carcinogenesis. Eur J Cancer Prevent 1995;4:45.

Bichler KH et al: Shistosomiasis: A critical review. Curr Opin Urol 2001;11:97.

Engels D et al: The global epidemiological situation of shistosomiasis and new approaches to control and research. Acta Trop 2002;82:139.

Ghoneim MA: Bilharziasis of the genitourinary tract. BJU Int 2002; 89(Suppl 1):22.

Hardin BM et al: Urinary tract shistosomiasis. J Urol 2010;184 (5):22136–22137.

Khalaf I et al: Urologic complications of genitourinary schistosomiasis. World J Urol 2012;30(1):31–38.

Mostafa MH et al: Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev 1999;12:97.

Naude JH: Reconstructive urology in the tropical and developing world: A personal perspective. BJU Int 2002;89(Suppl 1):31.

Shokeir AA: Renal transplantation: The impact of schistosomiasis. BJU Int 2001;88:915.

Stock JA et al: Urinary schistosomiasis in childhood. Urology 1994; 44:305.

Filariasis

De Vries CR: The role of the urologist in the treatment and elimination of lymphatic filariasis worldwide. BJU Int 2002;89(Suppl 1): 37.

Kehinde EO et al: Parasites of urological importance. Urol Int 2008; 81(1):1–13.

Kohli V et al: Filarial chyluria. Indian Pediatr 1994;31:451.

Pool MO et al: Bilateral excision of perinephric fat and fascia (Gerota's fasciectomy) in the treatment of intractable chyluria. J Urol 1991; 146:1374.

Punekar SV et al: Surgical disconnection of lymphorenal communication for chyluria: A 14-year experience. Br J Urol 1997;80:858.

Taylor MJ, Hoerauf A: A new approach to the treatment of filariasis. Curr Opin Infect Dis 2001;14:727.

Yagi S et al: Endoscopic treatment of refractory filarial chyluria: A preliminary report. J Urol 1998;159:1615.

Zhang X et al: Renal pedicle lymphatic disconnection for chyluria via retroperitoneoscopy and open surgery: Report of 53 cases with follow-up. J Urol 2005;174:1828.

Echinococcosis (Hydatid Disease)

Cagatay G et al: Isolated renal hydatidosis: Experience with 20 cases. J Urol 2003;169:186.

Cirenei A: Histopathology, clinical findings and treatment of renal hydatidosis. Ann Ital Chir 1997;68:275.

Migaleddu V et al: Imaging of renal hydatid cysts. Am J Roentgenol 1997;169:1339.

Pasaoglu E et al: Hydatid cysts of the kidney, seminal vesicle and gluteus muscle. Australas Radiol 1997;41:297.

Ranzini AC et al: Ultrasonographic diagnosis of pelvic echinococcosis: Case report and review of the literature. J Ultrasound Med 2002; 21:207.

Yeniyol CO et al: Primary cyst hydatid of adrenal: A case report. Int Urol Nephrol 2000;32:227.

Sexually Transmitted Infections

16

Kristin Madden, PharmD;
Amanda B. Reed-Maldonado, MD, FACS;
& John N. Krieger, MD

INTRODUCTION

A **sexually transmitted infection (STI)** is any infection that is acquired through sexual contact. There are more than 25 infectious organisms known to be transmitted primarily through sexual intercourse, including anal and oral sex. STIs may also be spread through blood contact, including the sharing of needles. The term **sexually transmitted infection (STI)** is a more encompassing term than **sexually transmitted disease (STD)**, as some infections may not cause any symptoms and may be curable. If the infection results in alteration of the typical function of the body, it is then termed a disease. For the purposes of this chapter, these two terms will be used interchangeably.

STI Epidemiology in the United States

The Centers for Disease Control and Prevention (CDC) estimates that on average there are 20 million new STIs diagnosed in the United States each year at cost of approximately $16 billion (Owusu-Edusel et al, 2013). Half of these cases are diagnosed in people aged 15–24 years (Satterwhite et al, 2013). According to the CDC's publication *Sexually Transmitted Diseases Surveillance, 2015,* the year 2015 was remarkable for the highest annual number of chlamydial infections ever reported—more than 1.5 million cases. In addition, the combined reported number of cases of chlamydia, gonorrhea, and syphilis (primary and secondary) reached a record high in 2015. From 2014 to 2015, the syphilis rate rose 19%, the gonorrhea rate rose 13%, and the chlamydia rate rose 6%. Chlamydia and gonorrhea rates continued to be highest amongst the 15–24-year-old age group, while the syphilis rate increased most among homosexual men (CDC, 2016). Unfortunately, despite increasing STI incidence in the United States, funding is decreasing for state and local STI programs. It is estimated that around 20 state and local STI programs closed in 2012 due to budget cuts leading to reduced clinical hours, contact tracing, and STI screening. If this trend continues, more STIs will go undiagnosed and untreated (Owusu-Edusel et al, 2013).

What caused this dramatic rise in reported STI rates? The apparent increase might reflect improved STI reporting, improved detection, or improved access to care. Alternatively, the increase could represent a true incidence in STI rates, which suggests decreased utilization of safer sex practices. The increase might also reflect decreased federal and state funding for STI education and prevention. The answer to this question remains unknown and largely speculative.

It has also been suggested that amplified communication networks, widespread social media, and ever-increasing employment of internet dating tools may contribute. Organizations including UNICEF in the Asia-Pacific region, the AIDS Health Foundation, and state and local governments in the United States have inferred that mobile dating applications may be responsible for the rapid increase in STI rates worldwide. These websites are thought to create an environment that facilitates unprotected, impulsive sexual encounters leading to increased rates of STIs (UNICEF, 2015). No studies have been conducted to substantiate these claims.

Some STIs are undiagnosed due to a lack of symptoms and, thus, remain untreated. Other STDs, including herpes simplex virus, trichomoniasis, and human papillomavirus are not routinely reported and tracked. Any person who engages in sexual activity is at risk for acquiring an STI, although some factors may increase a person's risk. These risk factors include unprotected sex, new or multiple sexual partners, being a man who has sex with men, history of an STIs, age between 15 and 24 years (Workowski et al, 2015), and waxing the pubic region (Osterberg et al, 2016).

STI Pathogens versus Syndromes

The usual approach to STIs and STDs considers the causative agents, emphasizing different classes, genera, species, and microbiological characteristics. This fits with most medical school curricula since the causative agents span the full spectrum of medical microbiology (viruses, bacteria, protozoa, ectoparasites). This classical approach often proves difficult in clinical practice, where many different types of agents must be considered in the differential diagnosis of an individual patient. This chapter takes a selective and practical approach. Because patients present with symptoms and signs that may be caused by pathogens from different microbiological classes, we will emphasize diagnosis and treatment of clinical syndromes in contrast to traditional teaching (Table 16–1). This is a large subject with much active research and a vast amount of literature. We stress the most important conditions encountered in urology: urethritis, epididymitis, genital ulcers, genital warts, plus a very brief discussion of human immunodeficiency virus (HIV) infection and relatively newer viruses including Ebola and Zika, which have both been shown to be sexually transmitted.

Table 16–1. Sexually transmitted disease (STD) syndromes.[a]

Syndrome	Causative agent
Urethritis and cervicitis[b]	Gonococcal infection Nongonococcal urethritis Chlamydial infection Mucopurulent cervicitis
Epididymitis[b]	Gonococcal infection Nongonococcal urethritis Chlamydial infection UTI bacteria
Genital ulcers[b]	Genital herpes simplex virus (HSV) Syphilis Chancroid Lymphogranuloma venereum Granuloma inguinale (donovanosis)
Human papillomavirus (HPV) infections[b]	Genital warts Subclinical genital HPV
HIV infection	HIV
Vaginal discharge	Bacterial vaginosis Trichomoniasis Vulvovaginal candidiasis
Pelvic inflammatory disease	Gonococcal infection Chlamydial infection Mixed infections
Ectoparasitic infections	Pediculosis pubis Scabies
Vaccine-preventable STDs	Hepatitis A Hepatitis B
Proctitis	Gonococcal infection Chlamydial infection Syphilis HSV
Proctocolitis	*Campylobacter* sp., *Shigella* sp., *Entamoeba histolytica*, and LGV serovars of *C. trachomatis*
Enteritis	Giardia

[a] Reproduced with permission from Centers for Disease Control and Prevention: 2015 Sexually transmitted disease treatment guidelines, MMWR Recomm Rep 2015;64(No. RR-13):1–40.

[b] Considered in this chapter.

URETHRITIS AND CERVICITIS

Urethritis in Men

Urethritis is urethral inflammation resulting from infectious or noninfectious etiologies (McCormack et al, 2000).

Patients may present with dysuria, urethral pruritus, and urethral discharge. On examination the discharge may be mucoid, purulent, or mucopurulent. The most commonly implicated pathogens are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. However, *Mycoplasma genitalium* has also been associated with urethritis (Bradshaw et al, 2006).

Laboratory testing for urethritis is recommended to document a specific infectious etiology and to direct treatment. In addition, a specific diagnosis may improve treatment compliance, streamline risk reduction interventions, and simplify partner notification. The CDC recommends nucleic acid amplification testing (NAATs) of a first-void urine sample as the preferred test for the detection of gonorrhea and chlamydia. If gonorrhea or chlamydial infection is detected, health department notification is required. If diagnostic testing is unavailable, patients should be empirically treated for both gonorrhea and chlamydia.

Complications of urethritis in men include epididymitis, prostatitis, disseminated gonococcal infection, and reactive arthritis. Complications of urethritis in females include pelvic inflammatory disease, ectopic pregnancy, and infertility secondary to tubal scarring (Tsevat et al, 2017). Complications in neonates include neonatal pneumonia and ophthalmia neonatorum, but these are infrequent due to implementation of prenatal screening and treatment during pregnancy.

A. Etiology of Urethritis

1. Gonococcal and chlamydial infections—Gonorrhea is diagnosed when *N. gonorrhoeae* is detected by Gram stain, nucleic acid amplification testing, or culture. Nongonococcal urethritis (NGU) is diagnosed when urethral secretions indicate inflammation without Gram-negative intracellular diplococci seen on microscopic examination. *C. trachomatis* is the primary cause of NGU, occurring in 15–40% of reported cases. The prevalence of chlamydial infection differs by age group, with a lower prevalence among older men. Documentation of chlamydial NGU is imperative due to the need for partner referral, evaluation, and treatment.

2. Other infectious causes—*Mycoplasma genitalium* accounts for 15–20% of NGU cases and 20–25% of nonchlamydial NGU cases in the United States. It is also the most common cause of persistent or recurrent nongonococcal, nonchlamydial NGU, accounting for approximately 30% of cases (Bradshaw et al, 2006). In general, *M. genitalium* is considered to be less common than *C. trachomatis*, but more common than *N. gonorrhoeae*. Nucleic acid amplification testing is the preferred method of testing for *M. genitalium* (Ross et al, 2009). Another pathogen associated with NGU is *Trichomonas vaginalis*, which is typically seen in heterosexual men (Hobbs et al, 2006). Other causes of NGU, such as herpes simplex virus (HSV), Epstein–Barr virus, and adenovirus, may be contracted through fellatio. Data supporting other *Mycoplasma* species and *Ureaplasma* as the causative agent for NGU are inconsistent. Specific diagnostic tests for these organisms are not routinely indicated but may be considered if the specific organism is suspected or if the prescribed therapy is ineffective.

B. Documenting Urethritis

It is important to document the presence of urethritis because some patients have urethral symptoms in the absence of inflammation or infection. Urethritis may be documented by the presence of any of the following clinical signs or tests: mucoid, purulent, or mucopurulent urethral discharge on physical examination; ≥2 leukocytes per oil immersion microscopic field of the Gram-stained urethral secretions; a positive leukocyte esterase test on first-void urine; or ≥10 leukocytes per high-power microscopic field of the first-void urine sediment. While point-of-care diagnostic tests should be utilized, nucleic acid amplification testing is the preferred test for documenting urethritis and evaluating the presence of chlamydial and gonococcal infections due to its high sensitivity and specificity (CDC, 2015).

Empiric antibiotic treatment of symptoms without documenting the presence of urethritis is recommended only if the patient is at high risk for infection and is unlikely to return for follow-up. Empiric antibiotic treatment should treat both gonococcal and chlamydial infection. Otherwise, treatment should be prescribed based on the specific organisms identified. Sex partners should be referred for appropriate evaluation and treatment.

C. Treatment of Gonococcal Infections

1. Epidemiology—There are an estimated 820,000 new gonococcal infections per year in the United States (see Satterwhite et al, 2013, in “Introduction” section above). In men, most infections cause symptoms that trigger the patient to seek treatment soon enough to prevent serious sequelae. However, this may not be soon enough to prevent transmission of infection to sex partners. In contrast, many gonococcal infections (and chlamydial infections) are asymptomatic in women and do not cause recognizable symptoms until the patient presents with complication, such as pelvic inflammatory disease (PID). Symptomatic and asymptomatic PID both result in tubal scarring that may lead to infertility and ectopic pregnancy (Mead et al, 2000).

2. Dual therapy for gonococcal and chlamydial infections—Dual therapy is recommended for both gonococcal and chlamydial infections because patients are often coinfected with both pathogens. Because of the increasingly resistant *N. gonorrhoeae* in the United States (Workowski et al, 2008), the CDC has stopped recommending fluoroquinolones (Perez-Losada et al, 2007; Khanam et al, 2016; Ahmed et al, 2010; Rahman et al, 2002) and cefixime as first-line treatment of gonorrhea (cefixime remains an alternative to first line). Additionally, it is thought that gonococcal strains with decreased or declining susceptibility to cefixime are likely also resistant to tetracyclines (see Workowski et al, 2015, in “Introduction” section above). In 2015, the CDC updated the gonorrhea treatment guidelines to reflect this and currently recommends dual treatment with the combination of ceftriaxone and azithromycin as the only first-line treatment.

3. Antimicrobial resistance—In the United States, *N. gonorrhoeae* has rapidly developed resistance to commonly prescribed antibiotics, such as ciprofloxacin and levofloxacin. In 2007, the CDC stopped recommending treatment with fluoroquinolones (Ghanem et al, 2005), leaving cephalosporins as the only first-line drugs. In 2010, the CDC updated its gonorrhea treatment guidelines to endorse double coverage with a cephalosporin plus either azithromycin or doxycycline, even if nucleic acid amplification testing for chlamydia was negative. Alarmingly, increasing numbers of resistant strains of gonorrhea have been documented in the United States and in other countries. There have been failures of cefixime and other oral cephalosporins in Asia, Europe, South Africa, and Canada, and failure of ceftriaxone reported for pharyngeal infections in Australia, Japan and Europe. Therefore, the CDC no longer recommends cefixime as a first-line agent for the treatment of gonococcal infections. Additionally, it is thought that gonococcal strains with decreased susceptibility to cefixime are likely resistant to tetracyclines, but remain susceptible to azithromycin.

4. Recommended regimens—Table 16–2 summarizes the recommended treatment regimens for uncomplicated gonococcal infections, that cure >99% of infections. First-line therapy is ceftriaxone 250 mg IM once plus azithroymcin 1 g in a single oral dose. Pharyngeal infections had a slightly lower rate of cure (98.9%) in clinical trials. Cefixime plus azithromycin is considered the alternative recommended regimen. In cases of azithromycin allergy, doxycycline (100 mg orally twice a day for 7 days) may be substituted. Spectinomycin (2 g as a single IM dose) may be considered for patients with uncomplicated urogenital and anorectal gonococcal infections, who cannot tolerate cephalosporins. Unfortunately, because spectinomycin is not produced in the United States, availability may be limited. Spectinomycin is also expensive, and it has limited efficacy (51.8%) against pharyngeal infections.

Routine test-of-cure cultures are not required for patients diagnosed with uncomplicated gonococcal infections.

Table 16–2. Urethritis, cervicitis, and related infections: recommended treatment regimens.

- Gonococcal infections
  - **Uncomplicated urethral, cervical and rectal infections**
    - Recommended: Ceftriaxone 250 mg as a single IM dose *plus* azithromycin 1 g in a single oral dose
    - Alternative (if ceftriaxone is unavailable): Cefixime 400 mg in a single oral dose *plus* azithromycin 1 g in a single oral dose
  - **Uncomplicated pharyngeal infections**
    - Ceftriaxone 250 mg as a single IM dose *plus* azithromycin 1 g in a single oral dose
- **Nongonococcal urethritis (chlamydial infections)**
  - Recommended: Azithromycin 1 g in a single oral dose *or* doxycycline 100 mg orally twice a day for 7 days
  - Alternative: Erythromycin base 500 mg orally 4 times daily *or* erythromycin ethylsuccinate 800 mg orally 4 times daily
  - Other alternatives: Levofloxacin 500 mg orally once a day *or* ofloxacin 300 mg twice a day orally for 7 days
- **Recurrent and persistent urethritis (NGU)**
  - *Mycoplasma genitalium*: Azithromycin 1 g in a single oral dose (if treated with doxycycline initially) *or* for azithromycin failure, moxifloxacin 400 mg orally once a day for 7 days
  - *Trichomoniasis vaginalis*: Metronidazole 2 g in a single oral dose *or* tinidazole 2 g in a single oral dose

However, patients should be reevaluated if symptoms persist after treatment, and any gonococci detected should undergo antimicrobial susceptibility testing. Infections identified after treatment are usually reinfections rather than treatment failures. Thus, all patients with a gonococcal diagnosis should be encouraged to refer their sex partners for evaluation and treatment. Retesting of patients for gonorrhea should ideally occur 3 months after treatment or if retesting is not possible at 3 months, as soon as the patient next presents for medical care within 12 months of initial treatment.

5. Complications—A few patients may develop complicated infections resulting from gonococcal bacteremia. These include disseminated gonococcal infection, perihepatitis, meningitis, or endocarditis. Disseminated gonococcal infection often causes petechial or pustular skin lesions, asymmetrical arthralgias, tenosynovitis, or septic arthritis. The *N. gonorrhoeae* strains that cause disseminated infection tend to cause minimal genital tract infection. All patients hospitalized with disseminated gonococcal infections should have antimicrobial susceptibility performed on any positive specimens in addition to consultation with an infectious disease specialist.

D. Treatment of Nongonococcal Urethritis (NGU)

Initiate treatment as soon as possible following NGU diagnosis (Shahmanesh et al, 2009). Single-dose, directly observed treatments have higher compliance rates than multiday regimens. Recommended regimens include either azithromycin or doxycycline for the treatment of chlamydial urethritis (Table 16–2). Alternative regimens, for patients who are allergic or cannot tolerate azithromycin or doxycycline, include erythromycin, levofloxacin, or ofloxacin for 7 days. Men diagnosed with NGU should be counseled to abstain from intercourse until both the patient and his partners have been completely treated to minimize the risk of transmission and reinfection.

Because of the high rates of reinfection, repeat testing should occur 3 months after treatment regardless of whether sexual partners were treated. Patients should also return for reevaluation if symptoms persist or recur after completion of treatment (Martin, 2008). Additionally, patients should be tested for HIV and syphilis upon diagnosis of NGU.

E. Treatment of Recurrent and Persistent Urethritis

Objective signs of urethritis should be documented before prescribing a repeat course of empiric therapy. Men with persistent or recurrent urethritis should be retreated with the initial regimen if they did not comply with treatment or if they were reexposed to an untreated sex partner. *M. genitalium* is the most common cause of persistent or recurrent NGU especially in those initially treated with doxycycline (Gaydos et al, 2009). Patients empirically treated with doxycycline receiving a diagnosis of persistent or recurrent NGU should be treated with a single dose of azithromycin. For those patients who failed treatment with azithromycin, treatment with 7 days of moxifloxacin is recommended.

Trichomoniasis vaginalis represents another documented cause of urethritis. Although not FDA-cleared in the United States, nucleic acid amplification testing is available and is more sensitive than cultures for detection of *T. vaginalis* in the urine. Presumptive treatment with metronidazole (2 g in a single oral dose) or tinidazole (2 g in a single oral dose) is recommended for men living in areas where *T. vaginalis* is prevalent (see Table 16–2).

▶ Mucopurulent Cervicitis in Women

A. Clinical Findings

Mucopurulent cervicitis in women holds many parallels to urethritis in men. Characteristically, patients have a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab sample. Easily induced endocervical bleeding is also common. Patients may present with complaints of abnormal vaginal discharge or abnormal vaginal bleeding, for example after intercourse, but many are asymptomatic.

B. Diagnosis and Treatment

In most cases of cervicitis no pathogen is isolated, especially in women at low risk of acquiring STDs, for example women >30 years of age. *C. trachomatis* and *N. gonorrhoeae* are the most commonly isolated organisms. Treatment should be guided by the results of testing for gonococcal and chlamydial infection, unless the patient is considered unlikely to return for follow-up. In such cases, empiric therapy should be given for both *C. trachomatis* and *N. gonorrhoeae*. In cases of persistent cervicitis after treatment with antimicrobial therapy, other factors should be considered including abnormal vaginal flora, frequent douching, and idiopathic inflammation. HIV and syphilis testing is recommended for women receiving a diagnosis of cervicitis.

EPIDIDYMITIS

Definition and Classification

Epididymitis is a clinical syndrome characterized by pain, swelling, and inflammation of the epididymis (Krieger, 2000). It may be further classified as "acute" if symptoms have been present for <6 weeks or "chronic" if symptoms have been present for ≥6 weeks (Nickel et al, 2000).

Etiology

Epididymitis is typically caused by sexually transmitted pathogens or by organisms known to cause urinary tract infection. *C. trachomatis* and *N. gonorrhoeae* are the most common causes of acute epididymitis among sexually active men <35 years of age. Enteric pathogens, such as *Escherichia coli*, may cause acute epididymitis in men who are the insertive partners during anal intercourse. Sexually transmitted epididymitis is usually associated with urethritis, which is often asymptomatic.

Most cases of acute epididymitis in men older than 35 years are associated with urinary tract infection. The most common pathogens are Gram-negative enteric bacteria. Epididymitis associated with urinary infection is more common among men who have anatomic abnormalities and those who have recently had urinary tract instrumentation. Therefore, evaluation of genitourinary tract anatomy is indicated for men with epididymitis associated with urinary tract infection.

Clinical Presentation and Diagnosis

Epididymitis is typically associated with unilateral hemiscrotal pain and tenderness, palpable epididymal swelling, and hydrocele (Cho et al, 2003). Sometimes the testis is also involved, a condition referred to as **epididymoorchitis**. Radionuclide scanning is considered the most accurate method to diagnose epididymitis, but it is not routinely available. Scrotal ultrasound may be employed if the diagnosis is uncertain from the history and physical examination or if there is concern about possible testis torsion. Because of the high sensitivity and specificity of documenting inflammation and the presence or absence of gonococcal infection, the preferred point-of-care diagnostic tests for acute epididymitis are Gram stain or methylene blue or gentian violet (MB/GV) stain of urethral secretions under microscopy with oil immersion. Diagnosis using this method is positive if ≥2 leukocytes are identified. The presence of a gonococcal infection may be established by documenting WBCs containing intracellular Gram-negative or purple diplococci on urethral Gram stain or MB/GV smear, respectively (see CDC, 2015 in "Urethritis and Cervicitis" section above).

Other diagnostic tests include positive leukocyte esterase test on first-void urine and high-power field microscopic examination of spun first-void urine with ≥10 WBC. Nucleic acid amplification testing should be performed on urine to test for gonococcal and chlamydial infections in any man with suspected acute epididymitis. Urine culture may have a higher yield in men with acute epididymitis caused by sexually transmitted enteric pathogens and in older men with acute epididymitis caused by typical genitourinary pathogens. HIV and other STI testing should be considered for patients presenting with acute epididymitis.

Treatment

Outpatient management is appropriate for most patients with epididymitis. Hospitalization should be considered if severe pain or high fever suggests torsion, testicular infarction, or abscess, or if the patient may be unable to comply with outpatient antibiotic regimens. Even prior to finalization of laboratory test results, empiric treatment based on the risk of chlamydia and gonorrhea and/or enteric organisms is recommended to prevent complications and transmission (Table 16–3). Adjunctive therapy includes bed rest, scrotal elevation, nonsteroidal anti-inflammatory agents, and pain management until inflammation improves and fever subsides.

Routine follow-up is recommended for acute epididymitis. Failure of treatment response within 3 days requires reevaluation of both the diagnosis and the treatment regimen (de Vries et al, 2001). If swelling and tenderness persist after antibiotic completion, reevaluation for alternative causes, such as testicular cancer, tuberculosis, infarction, abscess, or fungal epididymitis, should occur (Giannopoulos et al, 2001; Gul et al, 2009). HIV-infected patients with epididymitis

Table 16–3. Recommended treatment regimens for sexually transmitted acute epididymitis.

Suspected chlamydia and gonorrhea infection
Ceftriaxone 250 mg in a single IM dose *plus* doxycycline 100 mg orally twice a day for 10 days
Suspected chlamydia, gonorrhea, and enteric infection
Ceftriaxone 250 mg in a single IM dose *plus* levofloxacin 500 mg orally once a day for 10 days *or* ofloxacin 300 mg orally twice a day for 10 days
Suspected enteric infection only
Levofloxacin 500 mg orally once a day for 10 days *or* ofloxacin 300 mg orally twice a day for 10 days

should receive the same empiric therapy as HIV-negative men. However, fungal infections, atypical mycobacteria, and other opportunistic infections are more likely in immunosuppressed patients.

GENITAL ULCER DISEASES

In the United States, herpes simplex virus (HSV) is the most common cause of genital ulcers. Genital ulcers may also be caused by *Treponema pallidum* (syphilis) and less commonly chancroid (*Haemopilus ducreyi*), lymphogranuloma venereum (LGV; *C. trachomatis* serovars L1, L2, or L3), and granuloma inguinale (donovanosis; *Klebsiella granulomatis;* formerly known as *Calymmatobacterium granulomatis*) (Behets et al, 1999). Each of these ulcerative STIs is associated with an increased risk of HIV transmission and infection.

A diagnosis based solely on the history and physical examination findings is often inaccurate. Patients may be infected with more than one causative agent simultaneously. Testing should include evaluation for the most common causative agents including HSV, syphilis, and chancroid (in settings where chancroid is prevalent) (O'Farrell et al, 2008). These tests include serology, darkfield examination, or PCR testing for syphilis; culture or PCR testing for HSV; antibody specific serology for HSV; and a culture for *H. ducreyi.* Frequently, patients must be treated prior to confirmed laboratory test results, and the choice of initial therapy should be based on clinical presentation and epidemiologic data. Biopsy may be required in cases that are unusual or do not respond to initial therapy. Approximately 25% of patients who have a thorough diagnostic evaluation will have no laboratory confirmed diagnosis. HIV testing is also recommended for all patients who present with genital ulcers.

▶ Genital Herpes Simplex Virus (HSV) Infection

A. Clinical Presentation

Genital HSV is an incurable, chronic recurrent viral infection. It is estimated that around 87% of infected individuals are unaware that they are infected with HSV as they either are asymptomatic or have very mild symptoms that go unnoticed or are mistaken for skin condition (Wald et al, 2000; Fanfair et al, 2013; see also CDC, 2016 in "Introduction" section above). Characteristic genital lesions appear as one or more painful vesicles. Often, the genital lesions have evolved into pustules or ulcers when the patient is seen in the office.

B. Primary HSV Infection

With primary genital herpes, the ulcerative lesions persist for 4–15 days until crusting or reepithelization, or both, occurs. Pain, itching, vaginal or urethral discharge, and tender inguinal adenopathy are the predominant local symptoms. Primary HSV infection is associated with a high frequency and prolonged duration of systemic and local symptoms. Fever, headache, malaise, and myalgias are common. The clinical symptoms of pain and irritation from genital lesions gradually increase over the first 6–7 days, reach maximum intensity between days 7 and 11 of disease, and then recede gradually during the second or third week.

C. Recurrent HSV Infection

In contrast to first episodes, recurrent HSV infection is characterized by symptoms, signs, and anatomic sites localized to the genital region. Local symptoms, such as pain and itching, are typically milder than the symptoms of the initial infection, and the duration of the recurrent episode is typically shorter, ranging from 8 to 12 days.

D. Etiology

Two HSV serotypes cause genital ulcers, HSV1 and HSV2. An increasing number of cases of genital HSV infection are caused by HSV1 (Xu et al, 2016). However, recurrences of HSV1 infection are substantially less likely than recurrences of HSV2. Therefore, HSV2 cases accumulate in the population of patients with recurrent genital lesions. Typing the infecting strain has prognostic importance and is useful for patient counseling and education. Type-specific glycoprotein G-based serologic assays are the test of choice for determining HSV type. HSV antibody typing is recommended for patients who have recurrent or atypical genital symptoms with a negative HSV PCR or culture, a clinical diagnosis without lab confirmed diagnosis, and in patients whose partners have genital HSV. Testing is also recommended for HIV positive patients, men at risk (MSM) for HIV, and patients wanting to be screened for STDs. Patients with genital herpes have a two- to fourfold increased risk of acquiring HIV (Freeman et al, 2006; Barnabas et al, 2012; Corey et al, 2004).

E. Epidemiology

Serologic studies suggest that 50 million people in the United States are infected with genital HSV2. Most infections are mild or unrecognized. Therefore, most HSV-infected people do not receive this diagnosis. Such asymptomatic or mildly symptomatic persons shed virus intermittently in their genital tracts and can infect their sex partners. First-episode genital HSV infections are more likely to cause symptoms than recurrent infections. Occasional cases are severe enough to require hospitalization for complications such as disseminated infection, pneumonitis, hepatitis, meningitis, or encephalitis.

F. Treatment

Systemic antiviral therapy results in partial control of symptoms and signs of genital HSV infection. Treatment does not cure the infection or change the frequency or severity of recurrences after discontinuation of treatment. Three antiviral drugs have proved beneficial in randomized clinical trials: acyclovir, valacyclovir, and famciclovir (Table 16–4). Topical treatment with acyclovir has proved substantially less effective than systemic treatment and is not recommended.

Table 16–4. Genital ulcers: Recommended treatment regimens.

- Genital herpes
  - **First episode:**[a] Acyclovir 400 mg orally 3 times daily *or* (1) acyclovir 200 mg orally 5 times daily or valacyclovir 1 g orally twice a day, (2) famciclovir 250 mg orally 3 times daily for 7–10 days
  - **Severe disease**: Acyclovir 5–10 mg/kg body weight IV every 8 hours for 2–7 days or until clinical resolution
- Recurrent episodes
  - **Episodic recurrences:** Acyclovir 400 mg orally 3 times daily for 5 days or (1) acyclovir 800 mg orally twice daily for 5 days; (2) acyclovir 800 mg orally 3 times daily for 2 days; (3) valacyclovir 500 mg orally twice daily for 3 days; (4) valacyclovir 1 g orally once a day for 5 days; (5) famciclovir 125 mg orally twice daily for 5 days; (6) famciclovir 1 orally twice daily for 1 day, or famciclovir 500 mg orally once, followed by 250 mg orally twice daily for 2 days
  - **Daily suppressive therapy**: Acyclovir 400 mg orally twice a day; OR valacyclovir 500 mg orally once a day; valacyclovir 1g orally once a day; OR famciclovir 250 mg orally twice a day
- Syphilis
  - Primary and secondary
    - Benzathine penicillin G 2.4 million units as a single IM dose
  - Tertiary (except neurosyphilis)
    - Benzathine penicillin G 2.4 million units IM once a week for 3 weeks
  - Neurosyphilis
    - **Recommended**: Aqueous crystalline penicillin G 3–4 million units IV every 4 hours or 18–24 million units per day as a continuous infusion for 10–14 days
    - **Alternative:** Procaine penicillin G 2.4 million units IM once a day plus probenecid 500 mg orally 4 times daily for 10–14 days
  - Latent syphilis:
    - **Early**: Benzathine penicillin G 2.4 million units as a single IM dose
    - **Late or unknown duration**: Benzathine penicillin G 2.4 million units IM once a week for 3 weeks
- Chancroid
  - Azithromycin 1 g in a single oral dose or (1) ceftriaxone 250 mg as a single IM dose, (2) ciprofloxacin 500 mg orally twice daily for 3 days, (3) erythromycin base 500 mg orally 3 times daily for 7 days
- Granuloma inguinale[a]
  - **Recommended**: Azithromycin 1 g orally once a week for a minimum of 3 weeks; or azithromycin 500 mg orally once a day for a minimum of 3 weeks
  - **Alternative**: Doxycycline 100 mg orally twice a daily for a minimum of 3 weeks or (1) ciprofloxacin 750 mg orally twice daily for a minimum of 3 weeks, (2) erythromycin base 500 mg orally 4 times a daily for a minimum of 3 weeks, or (3) trimethoprim–sulfamethoxazole 1 double-strength tablet orally twice a day for a minimum of 3 weeks
- Lymphogranuloma enereum
  - **Recommended**: Doxycycline 100 mg orally twice daily for 21 days
  - **Alternative**: Erythromycin base 500 mg orally 4 times daily for 21 days

[a] Duration of therapy may be extended until healing is complete.

G. Initial HSV Episodes

Patients with first clinical episodes of genital HSV should receive antiviral treatment to expedite healing of genital lesions and shorten the duration of viral shedding. Patients should also be counseled about the natural history of genital herpes, the risks for sexual and perinatal transmission, and the methods to reduce transmission. Patients with severe disease should receive intravenous treatment with acyclovir.

H. Recurrent HSV Episodes

Most persons with first clinical episodes of genital HSV2 experience recurrent episodes. Treatment can shorten the duration of lesions and decrease recurrences (Wald et al, 2002). Thus, many patients can benefit from antiviral therapy, and this option should be discussed. There are two approaches to antiviral therapy for recurrent HSV: episodic treatment and daily suppressive treatment. Episodic therapy is beneficial for many patients with occasional recurrences. Such therapy is started during the prodrome or first day of lesion onset. Patients receiving episodic therapy should receive the medication or a prescription so that they may initiate treatment at the first symptom or sign of lesions. Traditionally, a 5-day course of treatment is recommended but a course as short as 1 day may be adequate depending on the patient and the antiviral medication selected (Table 16–4) (Wald et al, 2006).

I. Daily Therapy

Daily suppressive therapy is useful for patients who experience frequent recurrences (six or more per year) (Corey et al, 2004b). Therapy reduces the frequency of recurrences by 70–80%. Such treatment has been shown to be safe and effective for as long as 6 years with acyclovir and for as long as 1 year with both valacyclovir and famciclovir. Daily therapy does not appear to be associated with clinically significant HSV-drug resistance. Periodically, for example once a year, discontinuation of treatment should be considered since the frequency of recurrences often decreases with time.

▶ Syphilis

A. Clinical Presentation

Syphilis holds a special place in the history of medicine as "the great impostor" and "the great imitator." In 1897 Sir William Osler said, "Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you."

Syphilis, caused by the spirochete *Treponema pallidum*, is a complex systemic disease that is divided into primary, secondary, and tertiary stages. Primary syphilis is characterized by painless ulcers, or chancres, at the site of infection. Secondary syphilis usually develops several weeks after the primary chancre appears and is characterized by a papulosquamous skin rash, lymphadenopathy, or mucocutaneous lesions. Approximately 30% of untreated patients will progress to tertiary, or late, syphilis within 1–20 years. Tertiary syphilis is characterized by cardiovascular syphilis, gummatous lesions, tabes dorsalis, and general paresis. Patients may also develop asymptomatic, or latent, syphilis, that is detected with serologic testing. Latent syphilis acquired within the preceding 12 months is considered early latent. All other cases of latent syphilis are considered "late latent" or "syphilis of unknown duration."

Sexual transmission of syphilis is thought to occur only when mucocutaneous lesions are present. These manifestations are uncommon after the first year of infection in untreated patients. However, all people who have been sexually involved with an individual diagnosed with syphilis should be evaluated clinically and by serologic testing.

B. Diagnosis

Definitive diagnosis of early syphilis is made by darkfield microscopy of material from lesions or regional lymph nodes because antibodies may not be present yet, but darkfield microscopy is rarely performed today. Currently, presumptive diagnosis of early syphilis is most commonly made by serologic blood tests: (1) nontreponemal tests and (2) treponemal tests. Both types of tests are needed to confirm a diagnosis of syphilis. Nontreponemal tests (VDRL—venereal disease research laboratory; RPR—rapid plamsa reagin) are simple, inexpensive, and are often used for screening. These tests are not specific for syphilis, can produce false-positive results, and alone are insufficient for diagnosis. Treponemal tests (FTA-ABS—fluorescent treponemal antibody absorbed; TP-PA—treponemal passive particle agglutination; various EIAs, chemiluminescence immunoassays, immunoblots, and rapid treponemal assays) detect antibodies that are specific for syphilis. Treponemal antibodies appear earlier than nontreponemal antibodies, correlate poorly with disease activity, and usually remain detectable for life, even after successful treatment. Both serologic tests are necessary for diagnosis. False-positive nontreponemal tests occur with a variety of medical conditions. Nontreponemal tests correlate with disease activity, with results reported quantitatively. In general, a fourfold change in titer is considered significant. Thus, combination of both treponemal and nontreponemal tests is necessary for patient management.

Cerebrospinal fluid (CSF) is not routinely tested for primary and secondary syphilis. If the patient has neurologic or ophthalmic signs or symptoms, evidence of tertiary syphilis, treatment failure, or HIV with a CD4 count of ≤350 and/or a nontreponemal serologic test titer of ≥1:32, CSF should be evaluated promptly. CSF leukocyte count usually is elevated (>5 WBCs mm^{-3}) in patients with neurosyphilis. Patients with syphilis and signs or symptoms of ophthalmic involvement including uveitis, iritis, or neuroretinitis should have a slit-lamp examination performed. All individuals testing positive for syphilis should be tested for HIV. In areas with a high prevalence of HIV, a repeat HIV test should be performed after 3 months.

The entire genome of *T. pallidum* has been sequenced allowing for correlation of functional activities with this genetic information (Matejkova et al, 2008; Radolf and Desrosiers, 2009). Eradication of syphilis from the United States (CDC, 2007) and from the world (Rompalo, 2001) has been established as an important public health goal, although this goal may prove difficult to achieve because of high rates of infection in certain at-risk populations.

C. Treatment

For more than 40 years, penicillin has been the treatment of choice for syphilis (Table 16–4). Patients who are allergic to penicillin should receive a 2-week course of doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times a day) for primary or secondary syphilis, or a 4-week course for latent syphilis. Treatment results in healing of local lesions and prevents sexual transmission and late sequelae. Patients with syphilis should be tested for HIV infection. In areas with a high prevalence of HIV, this test should be repeated after 3 months if the initial HIV test is negative. Patients with syphilis and symptoms or signs of ophthalmic disease should have a slit-lamp examination. Patients with symptoms or signs of neurologic disease should have cerebrospinal fluid evaluation. Treatment failures occur with any regimen, and serologic testing should be repeated 6 and 12 months after initial treatment.

▶ Chancroid

A. Etiology and Clinical Presentation

Chancroid is a painful, acute genital ulcerative disease often associated with tender inguinal adenopathy ("bubo"). *Haemophilus ducreyi,* a Gram-negative facultative bacillus, is the causative agent (Janowicz et al, 2009). Although rates of chancroid have declined worldwide, chancroid still occurs in some parts of Africa and the Caribbean and outbreaks occur sporadically in the United States (Labandeira Rey et al, 2009). Like genital herpes and syphilis, chancroid is associated with an increased rate of HIV acquisition and transmission.

B. Diagnosis

Definitive diagnosis of chancroid requires identification of the causative bacterium, *H. ducreyi*, on a specialized media that is not widely available from commercial sources. Even when these specialized media are used, sensitivity is less than 80%. Therefore, a probable diagnosis of chancroid can be made if the following criteria are met: (1) the patient has at least one painful genital ulcer, (2) the appearance is typical of a chancroid ulcer, (3) there is no evidence of *T. pallidum* on darkfield examination or negative serologic test for syphilis performed at least 7 days after the onset of the ulcer, and (4) PCR test or culture of the ulcer exudate is negative for HSV.

C. Treatment

Multiple treatment regimens for chancroid are available (Table 16–4). Appropriate treatment of chancroid resolves the symptoms, cures the infection, and prevents disease transmission. Of note, intermediate resistance to both ciprofloxacin and erythromycin has been reported worldwide.

Uncircumcised and HIV-infected patients may not respond as well to treatment. The CDC recommends that patients be tested for both syphilis and HIV at the time of diagnosis with repeat testing after 3 months if initial results were negative.

Clinical follow-up should occur 3–7 days after initiation of therapy. If there is minimal or no clinical improvement, then another diagnosis or coinfection with another STD should be considered. Medication compliance and antibiotic resistance may contribute to incomplete response to treatment. Large ulcers or fluctuant lymphadenopathy may require more than 2 weeks for complete resolution. Occasionally, patients require incision and drainage or needle aspiration of fluctuant inguinal nodes.

▶ Lymphogranuloma Venereum (LGV)

A. Etiology and Clinical Presentation

Lymphogranuloma venereum (LGV) is caused by *C. trachomatis* (L1, L2, and L3). The disease is a rare cause of genital ulcers in the United States. Tender inguinal lymphadenopathy, femoral lymphadenopathy, or both is the characteristic clinical presentation in heterosexual men. A self-limited genital ulcer may occur at the site of inoculation, but often resolves prior to patients seeking treatment.

Women and homosexual men may present with inflammatory involvement of the perirectal and perianal lymphatics, colorectal strictures and fistulas, proctocolitis, or reactive arthropathy. Diagnosis is based on clinical judgement, epidemiologic data, and the exclusion of other etiologies. If present, genital lesions can be tested for *C. trachomatis* by culture, direct immunofluorescence, or nucleic acid detection.

B. Treatment

Patients presenting with symptoms consistent with LGV should be treated presumptively while awaiting diagnostic test results. Treatment with appropriate antibiotics (Table 16–4) will cure the infection and prevent ongoing tissue damage. However, scarring may occur due to tissue reaction to the infection. Inguinal adenopathy, known as "bubos," may require needle aspiration through intact skin or incision and drainage to prevent inguinal or femoral ulceration. Treatment with doxycycline is recommended for a minimum of 3 weeks but should extend until there is complete resolution of the presenting symptoms. Erythromycin may also be used as an alternative. Follow-up is also necessary until clinical signs and symptoms have completely resolved.

▶ Granuloma Inguinale (Donovanosis)

A. Etiology and Epidemiology

Granuloma inguinale is caused by *Klebsiella granulomatis*, a Gram-negative intracellular bacterium (formerly known as *Calymmatobacterium granulomatis*) (O'Farrell, 2002). This infection rarely occurs in the United States, but it is an important cause of genital ulcers in tropical and developing countries including India; Papua, New Guinea; the Caribbean; central Australia; and southern Africa.

B. Clinical Presentation

Granuloma inguinale presents with painless, progressive ulcers on the genitals or perineum. The genital lesions are highly vascular, with a "beefy red" appearance and tend to bleed. Patients seldom have inguinal lymphadenopathy, but subcutaneous granulomas may occur. This pathogen is hard to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy specimens. No molecular diagnostic test currently exists. Extragenital infection may occur and extend to the pelvis, bones, mouth, or intra-abdominal organs. Secondary bacterial infections may develop in the lesions. In addition, coinfection with other STIs may occur.

C. Treatment

Effective, prolonged treatment halts progressive tissue destruction and is necessary to facilitate granulation and reepithelization of the ulcers (Table 16–4). However, relapse may occur 6–18 months after seemingly effective antimicrobial therapy. Azithromycin is the recommended treatment for granuloma inguinale, although alternative treatments are available, including doxycycline, ciprofloxacin, erythromycin and trimethoprim-sulfamethoxazole. If improvement is not seen within the first few days of therapy, the addition of an aminoglycoside may be considered.

▶ Genital Warts

A. Etiology

Genital warts are caused by the human papillomaviruses (HPV). Approximately 100 HPV genotypes have been identified and at least 40 types of HPV are known to infect the genital area. Most genital HPV infections are asymptomatic, unrecognized, and resolve spontaneously. Depending on the size and anatomic location, visible external warts can be painful, friable, and pruritic. Most visible genital warts are caused by HPV type 6 or 11, as both types are assumed to cause 90% of nononcogenic HPV-associated anogential warts. These HPV types can also cause recurrent respiratory papillomatosis and warts on the cervix and within the vagina, urethra, and anus. Patients with external genital warts can be infected simultaneously with multiple HPV types (HPV types 16, 18, 31, 33, 35, etc). Most cervical, penile, vulvar, vaginal, anal, and oropharyngeal precancers and cancers are associated with HPV genotypes 16 and 18.

B. Diagnosis

Most often the diagnosis of genital warts can be made by inspection. Diagnosis can be confirmed by biopsy. However, biopsy is generally reserved for lesions with an uncertain diagnosis; lesions in immunocompromised patients; atypical lesions that are pigmented, fixed, indurated, or ulcerated; lesions unresponsive to standard therapy; or lesions that worsen during treatment. Routine use of HPV testing for genital warts is not recommended as results are not confirmatory and do not guide treatment.

C. Treatment

For visible genital warts, the primary goal of treatment is removal of symptomatic lesions. Treatment can result in wart-free periods in most patients. However, if left untreated genital warts, may remain unchanged, increase in number or size, or resolve spontaneously. No existing data suggest that therapy can eradicate or change the natural history of HPV infection (Cook and Brownell, 2008). Excision of exophytic warts may possibly decrease infectivity, but whether treatment reduces the probability of developing precancerous or cancerous lesions in the patient or sexual partners remains unknown.

Treatment decisions should be guided by the provider's experience and patient's preference. No treatment is superior to another or ideal for every case. Current treatments can be considered as patient-applied, provider-administered, or combination therapy (Table 16–5). In general, warts located on moist surfaces or in intertriginous areas respond better to topical treatments than do warts on drier surfaces. Most genital warts typically respond to treatment within 3 months.

Imiquimod is a topically active immune enhancer that stimulates the production of cytokines and interferon to produce local inflammation with eventual resolution of warts. Hypopigmentation and local inflammatory reactions (including redness, ulceration, and induration) have been reported with imiquimod use. Podofilox is an antimitotic drug that leads to wart necrosis. Patients may experience pain or local irritation after treatment. Sinecatechins is a green tea extract with an unknown mechanism of action in the clearance of genital warts. It may cause local burning, rash, erythema, or pruritus. Because of a lack of safety and efficacy data, sinecatechins is not recommended for immunocompromised or pregnant patients.

Provider-administered treatment with cryotherapy requires training and skill to prevent overtreatment or under treatment and to avoid adverse effects (Stefanaki et al, 2008). Pain is common after application of the liquid nitrogen, which causes necrosis of the warts. Trichloroacetic (TCA) and bichloroacetic (BCA) acids are widely used but have not been investigated thoroughly. Both TCA and BCA destroy genital warts through chemical coagulation of proteins and may damage surrounding tissue if not applied properly. Acid should be applied only to the wart and allowed to dry prior to the patient standing or sitting. If the patient experiences pain, the area treated may be neutralized using sodium bicarbonate (baking soda) or washed with liquid soap.

Surgical removal can eliminate warts in a single visit, but they may recur. Surgical removal may involve electrocautery, tangential scissor or shave excision, curettage, or laser surgery. All surgical methods require local anesthesia and are more time-consuming and expensive than other methods. Surgical approaches are most useful for patients who have a large number or a large volume of genital warts, if the diagnosis is uncertain, or if the patient is unresponsive to other treatments. Patients should be warned that scarring hypopigmentation, and hyperpigmentation are common and may occur after ablative therapy. Occasionally, patients experience chronic pain after such treatments.

Alternative HPV regimens, including podophyllin resin, intralesional interferon, and topical cidofovir, exist but are not recommended as there are limited data available regarding the safety and efficacy of these agents for the treatment of genital warts. The CDC no longer recommends podophyllin resin, as safer alternatives are available.

The treatment approach should be reevaluated if no improvement is observed after completion of a course of therapy or if severe adverse effects occur. Genital warts typically respond to therapy within 3 months. If no substantial improvement is seen after a course of therapy or if serious adverse effects occur, switching to a different treatment modality may be necessary.

Table 16–5. Recommended treatment regimens for external genital warts.

Patient-applied: Imiquimod 3.75% cream to lesions at bedtime every night or imiquimod 5% cream to lesions at bedtime 3 times per week (for ≤16 weeks), wash off after 6–10 hours or (1) podofilox 0.5% solution or gel to lesions twice a day for 3 days, followed by 4 days off therapy, repeat as needed for ≤4 cycles; or (2) sinecatechins[a] 15% ointment to lesions 3 times daily, do not wash off and use or ≤16 weeks if needed

Provider-administered: Cryotherapy with liquid nitrogen or cryoprobe, repeat as necessary every 1–2 weeks; or (1) trichloroacetic acid/bichloroacetic acid 80–90% solution, apply until white "frosting," repeat weekly as necessary; or (2) surgical removal (tangential scissor or shave excision, laser, curettage, or electrosurgery)

[a] Not recommended for use in immunocompromised or pregnant patients.

Recurrence of warts is common after all therapies, with most recurrences occurring within the first 3 months. Women should be counseled about the need for regular cervical cytologic screening. Examination of sex partners is unnecessary for management of external genital warts because the role of reinfection is probably minimal. However, sex partners of patients with genital warts may benefit from evaluation for genital warts and other STDs.

Use of HPV vaccines is recommended for both genders (Apter et al, 2015; Lehtinen et al, 2016; Park et al, 2015; Struyf et al, 2015). The vaccine series may be started as early as age 9 years and can be administered regardless of a history of anogenital warts, abnormal Pap/HPV tests, or anogenital precancerous lesions. The vaccines were recently approved for use in patients up to 45 years of age. In the United States, monitoring studies evaluating the quadrivalent vaccine have shown reductions in genital warts and HPV types contained in the vaccine (Munoz et al, 2009). The 9-valent HPV vaccine will be the only available HPV vaccine after the remaining quadrivalent vaccines are used or expire at the end of May 2017 (CDC, 2017).

SUBCLINICAL GENITAL HPV INFECTION

Subclinical HPV infection (infection without visible genital warts) is more common than visible genital lesions. Most cases are diagnosed indirectly by cervical cytology, colposcopy, or biopsy of genital skin, or by routine use of acetic acid soaks and examination with magnification for “acetowhite” areas. The consensus of expert opinion is to discourage routine examination for “acetowhitening.” This test has poor specificity for HPV infection and does not influence clinical management. In addition, the acetowhite test has many false-positive results in low-risk populations. Definitive diagnosis of subclinical HPV infection requires detection of HPV nucleic acid or capsid protein, but these tests are not recommended outside of research settings.

Treatment of subclinical HPV infection is not recommended in the absence of dysplasia. Diagnosis is often questionable because many of the diagnostic tests (eg, cytology, acetowhitening, colposcopy) correlate poorly with detection of HPV DNA or RNA. Furthermore, no therapy has been proved to eradicate infection. Subclinical HPV typically resolves spontaneously. HPV has been demonstrated in normal-appearing tissue adjacent to treated areas after aggressive surgical treatment.

HIV INFECTION: OVERVIEW OF DETECTION, INITIAL EVALUATION, AND REFERRAL

Infection with the human immunodeficiency virus (HIV) includes a wide clinical spectrum, ranging from asymptomatic infection to full-blown AIDS. The rate of clinical progression is highly variable with some persons progressing from HIV infection to AIDS within a few months and others remaining asymptomatic for decades. Overall, the median time from HIV infection to AIDS is around 11 years. In general, adults with HIV infection remain asymptomatic for prolonged periods. However, HIV viral replication continues during all stages of infection, with substantial increases in the viral burden during later stages of infection, accompanied by marked deterioration in immune functions.

Increasing awareness of risk factors for HIV infection has led to increased testing and earlier diagnosis for many patients. The primary risk factors for HIV infection are sexual contact with an HIV-infected person and sharing injecting-drug equipment.

Early diagnosis is important because treatment can slow the decline in immune function. HIV-infected persons with evidence of immune dysfunction are at risk for preventable infections. Prophylactic treatment can substantially reduce the risk for pneumonia (*Pneumocystis carinii* and bacterial), toxoplasma encephalitis, and mycobacterial disease (tuberculosis and *Mycobacterium avium* complex). Early diagnosis also facilitates patient counseling, which may reduce transmission. In addition, early diagnosis accelerates referral to a healthcare provider/facility experienced in care of HIV-infected persons.

Testing for HIV

Diagnostic testing for HIV should be offered to anyone at risk for infection, especially those seeking evaluation for STDs. Appropriate pre- and posttest counseling and informed consent should be included with the test procedure. Some states require documentation of informed consent for HIV testing. Usually, HIV infection is documented using an antigen–antibody combination or antibody immunoassay. The CDC recommends HIV1/HIV2 antigen–antibody immunoassay. Reactive screening test results are then confirmed using an HIV1/HIV2 antibody differentiation assay. All patients with reactive immunoassay results but negative antibody testing require additional RNA testing to determine whether the discordance represents acute HIV infection (ie, before antibody development). HIV home testing kits detect HIV antibodies only and, therefore, will not detect acute HIV infection. In the United States, almost all HIV infections are caused by HIV1. However, identification of HIV2 is important as monitoring and treatment differ.

Acute Retroviral Syndrome

This syndrome, characterized by acute symptoms and signs, including fever, malaise, lymphadenopathy, and skin rash, occurs in 50–90% of persons shortly after HIV infection and before antibody tests are positive. Acute HIV infection is highly infectious with extremely high viral concentrations in the plasma and genital secretions during this stage (Wawer et al, 2005). Suspicion of acute retroviral syndrome should prompt an antigen/antibody immunoassay or HIV RNA test in conjunction with an HIV antibody test. Data suggest that early initiation of treatment during this period can lower the

HIV viral burden, delay HIV-related complications, and perhaps promote immune reconstitution.

Initial Management of HIV Infection

It is advisable to refer HIV-infected persons to a single clinical resource for comprehensive care. Because of the limited availability of these facilities, it is often prudent to initiate evaluation and provide access to psychosocial services while arranging for referral and continuation of medical care.

Recently diagnosed HIV infection may not have been recently acquired, and persons newly diagnosed can be at any clinical stage of infection. Thus, it is important to be alert for signs and symptoms, such as fever, weight loss, diarrhea, oral candidiasis, cough, or shortness of breath, that suggest advanced infection. These findings indicate the need for urgent referral. In nonemergent situations, the recommended evaluation of a person with a newly diagnosed HIV infection includes a medication/social/family history, detailed medical history (past and present) that emphasizes sexual and substance abuse history, previous STDs, and specific HIV-related symptoms or diagnoses. The physical examination should include a pelvic examination with PAP smear in women and testing for all curable STIs (syphilis, gonorrhea, chlamydia, trichomonas, and others as clinically indicated) in all patients.

Recommended blood work includes complete blood count with platelet count; chemistry profile; lipid profile; testing for cytomegalovirus, anal HPV, toxoplasma antibody and hepatitis viral markers; syphilis serologic tests; HIV viral load, $CD4^+$ T-lymphocyte count; and HIV genotype testing. Other evaluations should include a tuberculin skin test and chest x-ray. Consideration should also be given to G6PD deficiency testing (due to increased likelihood to receive oxidant drugs and subsequent potential of hemolytic events), and tropism and HLA-B*5701 testing (to help guide choice of drug therapy) (Aberg et al, 2014). Finally, provision should be made for evaluation and management of sex partners and injecting-drug partners.

HIV Infection and Male Circumcision

Three large, well-conducted randomized clinical trials showed that adult male circumcision reduces HIV infection rates by approximately 60% in high-risk heterosexual populations (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007). These findings are consistent with substantial epidemiological data from the developing world and more limited data from the United States (Warner et al, 2009). Fortunately, the adult male circumcision procedures were done under local anesthesia with low complication rates (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007; Krieger et al, 2007). In addition, prospective data suggest that there was no adverse effect on male sexual function or satisfaction (Kigozi et al, 2008; Krieger et al, 2008). These data form the basis for implementation of programs to promote safe male circumcision in high-risk populations (Nagelkerke et al, 2007). This urological procedure is one of very few public health interventions that hold promise to reduce HIV infection rates.

EBOLA AND ZIKA VIRUSES

Both the Ebola virus and the Zika virus have recently caused outbreaks leading to devastating consequences. Neither virus causes specific genital symptoms, but both maybe sexually transmitted. A brief discussion of each follows to provide current information that may benefit both patient and provider.

Ebola Virus

A. Etiology and Epidemiology

Ebola, previously known as **Ebola hemorrhagic fever**, is caused by a virus of the family Filoviridae, genus *Ebolavirus*. There are five known Ebola virus species, four of which cause disease in humans. Ebola viruses are found in Africa with outbreaks occurring sporadically, most recently in 2014 in western African countries with the largest impact in Liberia, Sierra Leone, and Guinea.

Ebola is acquired through direct contact with blood or body fluids, including semen, urine, vomit, sweat, feces or the breast milk of a person sick with or who has died from Ebola. It may also be contracted from objects like needles, clothes, bedding, medical equipment, or syringes contaminated with the body fluids of a person with Ebola or someone who died of Ebola; infected fruit bats or primates; and possibly through oral, vaginal, or anal sex with a man who has recovered from the Ebola virus but continues to harbor the virus in body secretions. How long Ebola virus remains in the semen of survivors is unknown, and the virus is cleared at different rates ranging from roughly 3 to more than 9 months. Thus, it is recommended to avoid contact with semen from a man who has had the Ebola virus. It is not known if Ebola can be spread through sex or other contact with vaginal fluids from a woman who has survived Ebola.

B. Clinical Presentation

Symptoms generally appear 2–21 days after exposure to the virus and include fever (subjective or ≥100.4), headache, weakness, myalgias, vomiting, hemorrhage, or abdominal pain.

C. Diagnosis

Detection of the virus in the blood occurs only after the onset of symptoms. Although fever is associated with an increase in the viral load, it may take up to 3 days for the virus to reach detectable levels in the blood. In the United States, the Ebola virus is confirmed by the CDC through the use of enzyme-linked immunosorbent assay, virus isolation, or reverse transcriptase polymerase chain reaction tests.

D. Treatment

Current Ebola treatment is supportive care with emphasis on enteral hydration. There are no FDA-approved vaccines or antiviral drugs, but medications and vaccines are under development. The Sierra Leone Trial to Introduce a Vaccine against Ebola, which began in April 2015, is a phase 2 and 3 unblinded, individually randomized trial with phased introduction of the rVSV-ZEBOV (recombinant vesicular stomatitis virus *Zaire ebolavirus*) vaccine in healthcare providers and frontline staff, including ambulance and burial teams, to evaluate safety and efficacy (Agnandji et al, 2016). The trial is still ongoing. People who have recovered develop antibodies that may last for 10 years or more.

▶ Zika Virus

A. Etiology and Clinical Presentation

First discovered in 1947 and named after the Zika Forest in Uganda, the Zika virus was first reported to infect humans in 1952. Outbreaks have been reported in tropical Africa, Southeast Asia, and the Pacific Islands and may have occurred in many other locations but gone unrecognized because of the usually mild nature of the symptoms. Most recently, Zika has heavily impacted the Caribbean, South America, and Central America, with the CDC publishing multiple travel advisories. In addition, cautionary warnings were published for southern Florida and Brownsville, Texas, where local transmission was identified. In the United States and its territories from January 2015 to March 2017 over 43,000 Zika cases were reported to the CDC.

Zika virus is spread mainly through the bite of an infected *Aedes* mosquito. Generally, people infected with the Zika virus are asymptomatic or have mild symptoms including fever, rash, headache, joint pain, and conjunctivitis. Symptoms typically last a few days to a week with the virus remaining in the bloodstream of an infected individual for approximately 1 week. Zika is transmitted through blood transfusion, sexual intercourse, pregnancy from mother to fetus, and healthcare-associated exposure. The virus may be transmitted via sexual intercourse before presentation of symptoms, during symptoms, or after resolution of symptoms. The virus may also be passed sexually from a carrier who never develops symptoms. It is unknown how long the virus remains in the semen and vaginal fluids of infected individuals, but it is known that the virus remains in semen longer than other body fluids, such as blood and vaginal secretions.

Zika infection during pregnancy can cause severe birth defects including: microcephaly, other serious brain defects, defects of the eye, hearing deficits, impaired growth, and Guillain–Barré syndrome.

B. Diagnosis

Diagnosis of Zika virus is made by recent travel history, symptoms, and blood and urine testing. Currently, the only diagnostic tests for the Zika virus are the Trioplex Real-Time RT-PCR (rRT-PCR) assay and the Zika MAC-ELISA, which received Emergency Use Authorization (EUA) by the FDA.

C. Treatment

No specific antiviral medication exists to treat the Zika virus. Treatment is supportive, involving symptom management. Because of similarities with other viral infections, it is recommended that aspirin and other nonsteroidal anti-inflammatory medications be avoided to prevent possible hemorrhage due to dengue virus until a definitive diagnosis is made. To reduce the risk of transmission, infected men or those who have traveled to areas known to have the virus wait 6 months prior to having sexual intercourse without a condom or attempting conception.

CONCLUSIONS

Budget cuts will likely lead to continued reductions in the availability of services for STI screening and treatment. Thus, there is increased need for urologists to remain up to date on STI signs and symptoms to provide appropriate STI screening, treatment, and/or referrals when necessary. Patients presenting with potential STIs should be offered realistic risk reduction counseling and tools to decrease the danger of acquiring and transmitting STIs. Patients should also be encouraged to take an active role in their own healthcare and to make educated decisions about engaging in sexual activity and protecting themselves.

BIBLIOGRAPHY

Introduction

CDC (Centers for Disease Control and Prevention): Sexually Transmitted Disease Surveillance 2015. US Department of Health and Human Services, Atlanta, 2016. (Available online at: https://www.cdc.gov/std/stats15/.)

Osterberg EC, Gaither TW, Awad MA, et al: Correlation between pubic hair grooming and STIs: Results from a nationally representative probability sample. Sex Transm Infect, 2016.

Owusu-Edusei K Jr, Chesson HW, Gift TL, et al: The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. Sex Transm Dis 2013;40:197.

Satterwhite CL, Torrone E, Meites E, et al: Sexually transmitted infections among US women and men: Prevalence and incidence estimates, 2008. Sex Transm Dis 2013;40:187.

UNICEF East Asia and Pacific Regional Office and Asia Pacific Inter-Agency Task Team on Young Key Populations: Adolescents under the Radar in the Asia-Pacific AIDS Response. UNICEF East Asia Pacific Regional Office, Bangkok, December 2015. (Available online at: https://www.unicef.org/eapro/Adolescents_Under_the_Radar_final.pdf.)

Workowski KA, Bolan GA, CDC, et al: Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64:1.

Urethritis and Cervicitis

Ahmed MU, Chawdhury FA, Hossain M, et al: Monitoring antimicrobial susceptibility of Neisseria gonorrhoeae isolated from Bangladesh during 1997-2006: Emergence and pattern of drug-resistant isolates. J Health Popul Nutr 2010;28:443.

Bradshaw CS, Tabrizi SN, Read TR, et al: Etiologies of nongonococcal urethritis: Bacteria, viruses, and the association with orogenital exposure. J Infect Dis 2006;193:336.

CDC (Centers for Disease Control and Prevention), US Department of Health and Human Services: Sexually Transmitted Disease Surveillance 2015. US Department of Health and Human Services, Atlanta, 2016.

Gaydos C, Maldeis NE, Hardick A, et al: Mycoplasma genitalium compared to chlamydia, gonorrhoea and trichomonas as an aetiological agent of urethritis in men attending STD clinics. Sex Transm Infect 2009;85:438.

Ghanem KG, Giles JA, Zenilman JM: Fluoroquinolone-resistant Neisseria gonorrhoeae: The inevitable epidemic. Infect Dis Clin North Am, 2005; 19:351.

Hobbs MM, Lapple DM, Lawing LF, et al.: Methods for detection of Trichomonas vaginalis in the male partners of infected women: Implications for control of trichomoniasis. J Clin Microbiol 2006;44:3994.

Khanam R, Ahmed D, Rahman M, et al: Antimicrobial susceptibility of Neisseria gonorrhoeae in Bangladesh (2014 update). Antimicrob Agents Chemother 2016;60:4418.

Martin DH: Nongonococcal urethritis: New views through the prism of modern molecular microbiology. Curr Infect Dis Rep 2008;10:128.

McCormack WM, Rein M: Urethritis. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 5th ed., Vol. 1. Churchill-Livingstone, Philadelphia, 2000, pp. 1208–1218.

Mead P: Infections of the female pelvis. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 15th ed., Vol. 1. Churchill-Livingstone, Philadelphia, 2000, pp. 1235–1243.

Perez-Losada M, Crandall KA, Bash MC, et al: Distinguishing importation from diversification of quinolone-resistant Neisseria gonorrhoeae by molecular evolutionary analysis. BMC Evol Biol 2007;7:84.

Rahman M, Sultan Z, Monira S, et al: Antimicrobial susceptibility of Neisseria gonorrhoeae isolated in Bangladesh (1997 to 1999): Rapid shift to fluoroquinolone resistance. J Clin Microbiol 2002;40:2037.

Ross JD, Brown L, Saunders P, et al: Mycoplasma genitalium in asymptomatic patients: Implications for screening. Sex Transm Infect 2009;85:436.

Shahmanesh M, Moi H, Lassau F, et al: 2009 European guideline on the management of male non-gonococcal urethritis. Int J STD AIDS 2009; 2009;458.

Tsevat DG, Wiesenfeld HC, Parks C, et al: Sexually transmitted diseases and infertility. Am J Obstet Gynecol 2017;216:1.

Workowski KA, Berman SM, Douglas JM Jr: Emerging antimicrobial resistance in Neisseria gonorrhoeae: Urgent need to strengthen prevention strategies. Ann Intern Med, 2008;148:606.

Epididymitis

Cho YH, Jung J, Lee KH, et al: Clinical features of patients with Behcet's disease and epididymitis. J Urol 2003;170:1231.

de Vries M, van Der Horst I, van Der Kleij F, et al: Polyarteritis nodosa presenting as an acute bilateral epididymitis. Arch Intern Med 2001;161:1008.

Giannopoulos A, Giamarellos-Bourboulis EJ, Adamakis I, et al: Epididymitis caused by Candida glabrata: A novel infection in diabetic patients? Diabetes Care 2001;24:2003.

Gul HC, Akyol I, Sen B, et al: Epididymoorchitis due to Brucella melitensis: Review of 19 patients. Urol Int 2009;82:158.

Krieger J: Prostatitis, epididymitis and orchitis. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectioius Diseases. 15th ed. Philadelphia: Churchill-Livingstone, 2000, pp. 1243–1251.

Nickel JC, Siemens DR, Nickel KR, et al: The patient with chronic epididymitis: Characterization of an enigmatic syndrome. J Urol 2002;167:1701.

Genital Ulcer Diseases

Apter D, Wheeler CM, Paavonen J, et al: Efficacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precancer in young women: Final event-driven analysis of the randomized, double-blind PATRICIA trial. Clin Vaccine Immunol 2015;22:361.

Barnabas RV, Celum C: Infectious co-factors in HIV-1 transmission herpes simplex virus type-2 and HIV-1: New insights and interventions. Curr HIV Res 2012;10:228.

Behets FM, Andriamiadana J, Randrianasolo D, et al: Chancroid, primary syphilis, genital herpes, and lymphogranuloma venereum in Antananarivo, Madagascar. J Infect Dis 1999;180:1382.

CDC (Centers for Disease Control and Prevention): Human Papillomavirus (HPV) Gardasil® Vaccine Information Statement. (Available online at: https://www.cdc.gov/vaccines/hcp/vis/vis-statements/hpv-gardasil.pdf; accessed: 3/10/17.)

CDC (Centers for Disease Control and Prevention): Congenital syphilis—United States, 2002. MMWR Morb Mortal Wkly Rep 2004;53:716.

Cook K, Brownell I: Treatments for genital warts. J Drugs Dermatol 2008;7:801.

Corey L, Wald A, Celum CL, et al: The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: A review of two overlapping epidemics. J Acquir Immune Defic Syndr 2004; 35:435.

Corey L, Wald A, Patel R, et al: Once-daily valacyclovir to reduce the risk of transmission of genital herpes. New Engl J Med 2004;350:11.

Fanfair RN, Zaidi A, Taylor LD, et al: Trends in seroprevalence of herpes simplex virus type 2 among non-Hispanic blacks and non-Hispanic whites aged 14 to 49 years--United States, 1988 to 2010. Sex Transm Dis 2013;40:860.

Freeman EE, Weiss HA, Glynn JR, et al: Herpes simplex virus 2 infection increases HIV acquisition in men and women: Systematic review and meta-analysis of longitudinal studies. AIDS 2006;20:73.

Janowicz DM, Ofner S, Katz BP, et al: Experimental infection of human volunteers with Haemophilus ducreyi: Fifteen years of clinical data and experience. J Infect Dis 2009;199:1671.

Labandeira-Rey M, Janowicz DM, Blick RJ, et al: Inactivation of the Haemophilus ducreyi luxS gene affects the virulence of this pathogen in human subjects. J Infect Dis 2009;200:409.

Lehtinen M., Eriksson T, Apter D, et al: Safety of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in adolescents aged 12-15 years: Interim analysis of a large community-randomized controlled trial. Hum Vaccin Immunother 2016;12:3177.

Matejkova P, Strouhal M, Smajs D, et al: Complete genome sequence of Treponema pallidum ssp. pallidum strain SS14 determined with oligonucleotide arrays. BMC Microbiol 2008;8:76.

Munoz N, Manalastas R Jr, Pitisuttithum P, et al: Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: A randomised, double-blind trial. Lancet 2009;373:1949.

O'Farrell N, Morison L, Moodley P, et al: Genital ulcers and concomitant complaints in men attending a sexually transmitted infections clinic: Implications for sexually transmitted infections management. Sex Transm Dis 2008;35:545.

O'Farrell N: Donovanosis. Sex Transm Infect 2002;78:452.

Park IU, Introcaso C, Dunne EF: Human papillomavirus and genital warts: A review of the evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis 2015;61(Suppl 8): S849.

Radolf JD, Desrosiers DC: Treponema pallidum, the stealth pathogen, changes, but how? Mol Microbiol 2009;72:1081.

Rompalo AM: Can syphilis be eradicated from the world? Curr Opin Infect Dis 2001;14:41.

Stefanaki C, Katzouranis I, Lagogianni E, et al: Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. Int J STD AIDS 2008;19:441.

Struyf F, Colau B, Wheeler CM, et al: Post hoc analysis of the PATRICIA randomized trial of the efficacy of human papillomavirus type 16 (HPV-16)/HPV-18 AS04-adjuvanted vaccine against incident and persistent infection with nonvaccine oncogenic HPV types using an alternative multiplex type-specific PCR assay for HPV DNA. Clin Vaccine Immunol 2015;22:235.

Wald A, Carrell D, Remington M, et al: Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. Clin Infect Dis 2002;34:944.

Wald A, Selke S, Warren T, et al: Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. Sex Transm Dis 2006;33:529.

Wald A, Zeh J, Selke S, et al: Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. New Engl J Med 2000;342:844.

Xu F, Sternberg MR, Kottiri BJ, et al: Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA 2006;296:964.

HIV Infection

Aberg JA, Gallant JE, Ghanem KG, et al: Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2014;58:1.

Auvert B, Taljaard D, Lagarde E, et al: Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. PLoS Med 2005;2:e298.

Bailey RC, Moses S, Parker CB, et al: Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomised controlled trial. Lancet 2007;369: 643.

Gray RH, Kigozi G, Serwadda D, et al: Male circumcision for HIV prevention in men in Rakai, Uganda: A randomised trial. Lancet 2007;369:657.

Kigozi G, Watya S, Polis CB, et al: The effect of male circumcision on sexual satisfaction and function, results from a randomized trial of male circumcision for human immunodeficiency virus prevention, Rakai, Uganda. BJU Int 2008;101: 65.

Krieger JN, Mehta SD, Bailey RC, et al: Adult male circumcision: Effects on sexual function and sexual satisfaction in Kisumu, Kenya. J Sex Med 2008;5:2610.

Krieger JN, Bailey RC, Opeya JC, et al: Adult male circumcision outcomes: Experience in a developing country setting. Urol Int 2007;78:235.

Nagelkerke NJ, Moses S, de Vlas SJ, et al: Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. BMC Infect Dis 2007;7:16.

Warner L, Ghanem KG, Newman DR, et al: Male circumcision and risk of HIV infection among heterosexual African American men attending Baltimore sexually transmitted disease clinics. J Infect Dis 2009;199:59.

Wawer MJ, Gray RH, Sewankambo NK, et al: Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005;191:1403.

Ebola and Zika Viruses

Agnandji ST, Huttner A, Zinser ME, et al: Phase 1 trials of rVSV Ebola vaccine in Africa and Europe. New Engl J Med 2016;374:1647.

This page intentionally left blank

17

Urinary Stone Disease

Marshall L. Stoller, MD

Urinary calculi are the third most common affliction of the urinary tract, exceeded only by urinary tract infections and pathologic conditions of the prostate. They are common in both animals and humans. The nomenclature associated with urinary stone disease arises from a variety of disciplines. Struvite stones, for example, composed of magnesium ammonium phosphate hexahydrate, are named in honor of H. C. G. von Struve (1772–1851), a Russian naturalist. Before the time of von Struve, the stones were referred to as **guanite**, because magnesium ammonium phosphate is prominent in bat droppings. Calcium oxalate dihydrate is frequently referred to as **weddellite**, because it was commonly found in floor samples collected from the Weddell Sea off Antarctica. The history of the nomenclature associated with urinary stone disease is as intriguing as that of the development of the interventional techniques used in their treatment.

Urinary stones have plagued humans since the earliest records of civilization. The etiology of stones remains speculative. If urinary constituents are similar from each kidney and if there is no evidence of obstruction, why do most stones present in a unilateral fashion? Why do not small stones pass uneventfully down the ureter early in their development? Is there a continuum between nephrocalcinosis and nephrolithiasis, or are they unique and distinct? Why do some people form one large stone and others form multiple small calculi? There is much speculation concerning these and other questions.

Advances in the surgical treatment of urinary stones have outpaced our understanding of their etiology. As clinicians, we are concerned with an expedient diagnosis and efficient treatment. Equally important is a thorough metabolic evaluation directing appropriate medical therapy and lifestyle changes to help reduce recurrent stone disease. Without such follow-up and medical intervention, stone recurrence rates can be as high as 50% within 5 years. Uric acid calculi and cystine stones can recur much more frequently. Physicians look forward to gaining a better understanding of this multifactorial disease process in hopes of developing more effective prophylaxis.

RENAL AND URETERAL STONES

Etiology

Mineralization in all biologic systems has a common theme in that the crystals and matrix are intertwined. Urinary stones are no exception; they are polycrystalline aggregates composed of varying amounts of crystalloid and organic matrix. Theories to explain urinary stone disease are incomplete.

Stone formation requires supersaturated urine. Supersaturation depends on urinary pH, ionic strength, solute concentration, and complexation. Urinary constituents may change dramatically during different physiologic states from a relatively acid urine in a early-morning void to an alkaline tide noted after meals. Ionic strength is determined primarily by the relative concentration of monovalent ions. As ionic strength increases, the activity coefficient decreases. The activity coefficient reflects the availability of a particular ion.

The role of solute concentrations is clear: The greater the concentration of two ions, the more likely they are to precipitate. Low ion concentrations result in undersaturation and increased solubility. As ion concentrations increase, their activity product reaches a specific point termed the **solubility product (*K*sp)**. Concentrations above this point are metastable and are capable of initiating crystal growth and heterogeneous nucleation. As solutions become more concentrated, the activity product eventually reaches the formation product (K_{fp}). Supersaturation levels beyond this point are unstable, and spontaneous homogeneous nucleation may occur.

Multiplying two ion concentrations reveals the concentration product. The concentration products of most ions are greater than established solubility products. Other factors must play major roles in the development of urinary calculi, including complexation. Complexation influences the availability of specific ions. For instance, sodium complexes with oxalate and decreases its free ionic form, while sulfates can complex with calcium. Crystal formation is modified by a variety of other substances found in the urinary tract, including magnesium, citrate, pyrophosphate, and a variety of trace metals. These inhibitors may act at the active crystal growth sites or as inhibitors in solution (as with citrate).

Nucleation is the first step in the formation of urinary stones. An everyday example of nucleation is observed in a pot of water just prior to boiling; small bubbles are seen at the bottom of the pot prior to actually boiling. The nucleation theory for urinary stone disease suggests that urinary stones originate from crystals or other nidi immersed in supersaturated urine. This theory is challenged by the same arguments that support it. Stones do not always form in patients who are hyperexcretors or who are at risk for dehydration. Additionally, up to a third of stone formers' 24-hour urine collections are completely normal with respect to stone-forming ion concentrations.

The crystal inhibitor theory claims that calculi form in the absence or low concentration of natural stone inhibitors, including magnesium, citrate, pyrophosphate, and a variety of trace metals. This theory does not have absolute validity, since many people lacking such inhibitors may never form stones, and others with an abundance of inhibitors may, paradoxically, form them.

A. Crystal Component

Stones are composed primarily of a crystalline component. Crystals of adequate size and transparency are easily identified under a polarizing microscope. X-ray diffraction is preferred to assess the geometry and architecture of calculi. A group of stones from the same geographic location or the same historical time period typically have crystalline constituents that are common.

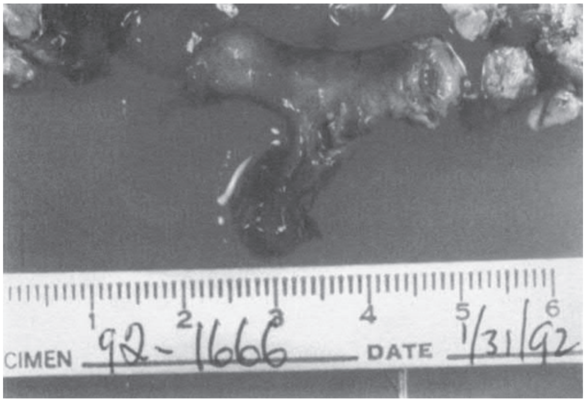
Multiple steps are involved in crystal formation, including nucleation, growth, and aggregation. Nucleation initiates the stone process and may be induced by a variety of substances, including proteinaceous matrix, crystals, foreign bodies, and other particulate tissues. Heterogeneous nucleation (epitaxy), which requires less thermodynamic energy and may occur in less saturated urine, is a common theme in stone formation. It should be suspected whenever an oriented conglomerate is found. A crystal of one type thereby serves as a nidus for the nucleation of another type with a similar crystal lattice. This is frequently seen with uric acid crystals initiating calcium oxalate formation. It takes time for these early nidi to grow or aggregate to form a stone incapable of passing with ease through the urinary tract.

How these early crystalline structures are retained in the upper urinary tract without uneventful passage down the ureter is unknown. The theory of mass precipitation or intranephronic calculosis suggests that the distal tubules or collecting ducts, or both, become plugged with crystals, thereby establishing an environment of stasis, ripe for further stone growth. This explanation is unsatisfactory; tubules are conical in shape and enlarge as they enter the papilla (ducts of Bellini), thereby reducing the possibility of ductal obstruction. In addition, urine transit time from the glomerulus into the renal pelvis is only a few minutes, making crystal aggregation and growth within the uriniferous tubules unlikely.

The fixed-particle theory postulates that formed crystals are somehow retained within cells or beneath tubular epithelium. Alexander Randall documented whitish-yellow precipitations of crystalline substances at the tips of renal papillae. New data suggest that early Randall plaques occur within the tubules (vascular and urinary) in proximal and peripheral aspects of the papilla (unseen during endoscopy) in contrast to the plaques visible during endoscopy that are interstitial in origin. When these distal plaques mature, they can erode into tubules and the collecting system and ultimately form urinary stones. Much novel research has been undertaken to better understand the etiology of these Randall plaques. The tips of the plaques can be appreciated near the center of renal papilla during endoscopy of the upper urinary tract. Carr hypothesized that calculi form in obstructed lymphatics and then rupture into adjacent fornices of a calyx. Arguing against Carr's theory are the grossly visible early stone elements in areas remote from fornices.

B. Matrix Component

The amount of the noncrystalline, matrix component of urinary stones varies with stone type, commonly ranging from 2% to 10% by weight. It is composed predominantly of protein, with small amounts of hexose and hexosamine. An unusual type of stone called a **matrix calculus** can be associated with previous kidney surgery or chronic urinary tract infections and has a gelatinous texture (Figure 17–1)



▲ **Figure 17–1.** Gross picture of matrix calculus percutaneously extracted after extracorporeal shockwave lithotripsy failure.

Histologic inspection reveals laminations with scant calcifications. On plain abdominal radiographs, matrix calculi are usually radiolucent and can be confused with other filling defects, including blood clots, upper tract tumors, and fungal bezoars. Noncontrast computed tomography (CT) reveals calcifications and can help confirm the diagnosis. The role of matrix in the initiation of ordinary urinary stones as well as matrix stones is unknown. It may serve as a nidus for crystal aggregation or as a naturally occurring glue to adhere small crystal components and thereby hinder uneventful passage down the urinary tract. Alternatively, matrix may have an inhibitory role in stone formation or may be an innocent bystander, playing no active role in stone formation.

Urinary Ions

A. Calcium

Calcium is a major ion present in urinary crystals. The risk of urinary stones increases as fractional calcium absorption from the gut increases; calcium absorption from the gut decreases with increased calcium intake. Only 50% of plasma calcium is ionized and available for filtration at the glomerulus. More than 95% of the calcium filtered at the glomerulus is reabsorbed at both the proximal and distal tubules and limited amounts in the collecting duct. Less than 2% is excreted in the urine; typically, patients will excrete <4 mg/kg in 24 hours. Diuretic medications may exert a hypocalciuric effect by further decreasing calcium excretion. Many factors influence the availability of calcium in solution, including complexation with citrate, phosphate, and sulfate. An increase in monosodium urates and a decrease in urinary pH further interfere with this complexation and therefore promote crystal aggregation.

B. Oxalate

Oxalate is a normal waste product of metabolism and is relatively insoluble. Normally, approximately 10–15% of oxalate found in the urine originates from the diet; the vast majority is a metabolic by-product. Most of the oxalate that enters the large bowel is consumed by bacterial decomposition. Oxalobacter formigenes may alter the availability of oxalate absorption. Diet, however, can have an impact on the amount of oxalate found in the urine. Once absorbed from the small bowel, oxalate is not metabolized and is excreted almost exclusively by the proximal tubule. The presence of calcium within the bowel lumen is an important factor influencing the amount of oxalate that is absorbed. The control of oxalate in the urine plays a pivotal role in the formation of calcium oxalate calculi. Normal excretion ranges from 20 to 45 mg/day and does not change significantly with age. Excretion is higher during the day when one eats. Small changes in oxalate levels in the urine can have a dramatic impact on the supersaturation of calcium oxalate. The important precursors of oxalate are glycine and ascorbic acid; however, the impact of ingested vitamin C (<2 g/day) is negligible.

Hyperoxaluria may develop in patients with bowel disorders, particularly inflammatory bowel disease, small-bowel resection, and bowel bypass. Renal calculi develop in 5–10% of patients with these conditions. Chronic diarrhea with fatty stools results in a saponification process. Intraluminal calcium binds to the fat, thereby becoming unavailable to bind to oxalate. The unbound oxalate is readily absorbed from the gut and increases urinary oxalate levels.

Excessive oxalate may occur secondary to the accidental or deliberate ingestion of ethylene glycol (partial oxidation to oxalate). This may result in diffuse and massive deposition of calcium oxalate crystals and may occasionally lead to renal failure.

C. Phosphate

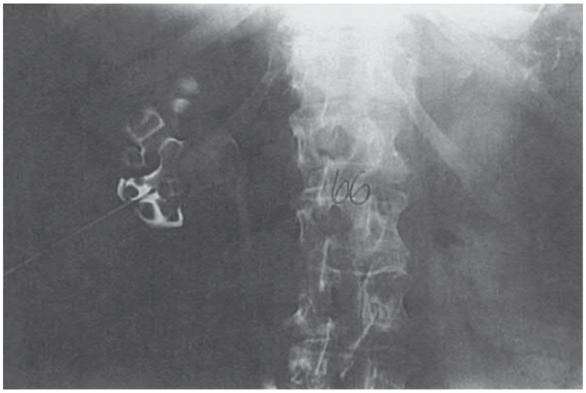
Phosphate is an important buffer and complexes with calcium in urine. It is a key component in calcium phosphate and magnesium ammonium phosphate stones. The excretion of urinary phosphate in normal adults is related to the amount of dietary phosphate (especially in meats, dairy products, and vegetables). The small amount of phosphate filtered by the glomerulus is predominantly reabsorbed in the proximal tubule. Parathyroid hormone inhibits this reabsorption. The predominant crystal found in patients with hyperparathyroidism is phosphate, in the form of hydroxyapatite, amorphous calcium phosphate, and carbonate apatite.

D. Uric Acid

Uric acid is the by-product of purine metabolism. The pK_a of uric acid is 5.75. Undissociated uric acid predominates with pH values less than this. Elevated pH values increase urate, which is soluble. Approximately 10% of the filtered uric acid finds its way into the urine. Other defects in purine metabolism may result in urinary stone disease. Rarely, a defect in xanthine dehydrogenase results in increased levels of xanthine; the xanthine may precipitate in urine, resulting in stone formation. Unusual alterations in adenine metabolism may result in the production of 2,8-dihydroxyadeninuria, which is poorly soluble in urine and may develop into a urinary stone. This results from a deficiency of adenine phosphoribosyltransferase (APRT). Pure uric acid crystals and calculi are relatively radiolucent and may not be identified on plain abdominal films (Figure 17–2). They are visible on noncontrast CT images and are suggestive when found to have low Hounsfield units (HU). Some uric acid calculi may be partially radiopaque, however, because of associated calcium phosphate deposits.

E. Sodium

Although not identified as one of the major constituents of most urinary calculi, sodium plays an important role in regulating the crystallization of calcium salts in urine. Sodium is found in higher than expected concentrations in the core of



▲ **Figure 17–2.** Radiolucent right staghorn renal calculus appreciated after percutaneous injection of radiocontrast material. This uric acid stone was effectively removed in a single percutaneous procedure. Postoperative urinary alkalinization has provided effective prophylaxis.

renal calculi and may play a role in initiating crystal development and aggregation. High dietary sodium intake increases urinary calcium excretion and increases the urinary levels of monosodium urates that promote stone growth. This reduces the ability of urine to inhibit calcium oxalate crystal agglomeration. These effects are thought to be due to a sodium-induced increase in bicarbonaturia and a decrease in serum bicarbonate. Interestingly, increased dietary sodium intake increases one's thirst and increases voided volumes. Conversely, a reduction in dietary sodium helps reduce recurrent calcium nephrolithiasis.

F. Citrate

Citrate is a key factor affecting the development of calcium urinary stones. A deficiency commonly is associated with stone formation in those with chronic diarrhea or renal tubular acidosis type I (distal tubular defect) and in patients prescribed chronic thiazide therapy. Citrate plays a pivotal role in the citric acid cycle in renal cells. Metabolic stimuli that consume this product (as with intracellular metabolic acidosis due to fasting, hypokalemia, or hypomagnesemia) reduce the urinary excretion of citrate. Estrogen increases citrate excretion and may be a factor in reducing the incidence of stones in women, especially during pregnancy. Alkalosis also increases citrate excretion.

G. Magnesium

Dietary magnesium deficiency is associated with an increased incidence of urinary stone disease. Magnesium is a component of struvite calculi. Experimentally, lack of dietary magnesium is associated with increased calcium oxalate stone formation and calcium oxalate crystalluria. The exact mechanism whereby magnesium exerts its effect is undefined. Dietary magnesium supplements typically do not protect against stone formation.

H. Sulfate

Urinary sulfates may help prevent urinary calculi. They can complex with calcium. These sulfates occur primarily as components of longer urinary proteins, such as chondroitin sulfate and heparin sulfate.

I. Other Urinary Stone Inhibitors

Inhibitors of urinary stone formation other than citrate, magnesium, and sulfates have been identified. These consist predominantly of urinary proteins and other macromolecules such as glycosaminoglycans, pyrophosphates, and uropontin. Although citrate appears to be the most active inhibitory component in urine, these substances demonstrate a substantial role in preventing urine crystal formation. The *N*-terminal amino acid sequence and the acidic amino acid content of these protein inhibitors, especially their high aspartic acid content, appear to play pivotal inhibitory roles. Fluoride may be an inhibitor of urinary stone formation.

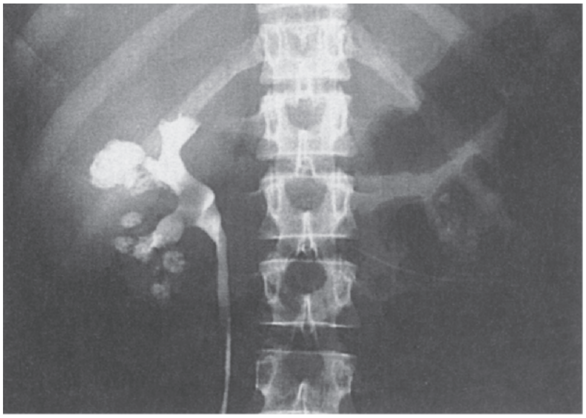
▶ Stone Varieties

A. Calcium Calculi

Calcifications can occur and accumulate in the collecting system, resulting in nephrolithiasis. Approximately 80–85% of all urinary stones are calcareous.

Calcium nephrolithiasis is most commonly due to elevated urinary calcium, elevated urinary uric acid, elevated urinary oxalate, or a decreased level of urinary citrate. Hypercalciuria is found as a solitary defect in 12% of patients and in combination with other defects in an additional 18%. Hyperuricosuria is identified as a solitary defect in 8% of patients and associated with additional defects in 16%. Elevated urinary oxalate is found as a solitary finding in 5% of patients and as a combined defect in 16%. Finally, decreased urinary citrate is found as an isolated defect in 17% of patients and as a combined defect in an additional 20%. Approximately one-third of patients undergoing a full metabolic evaluation will exhibit no identifiable metabolic defect.

Symptoms from stones are secondary to obstruction, with resultant pain, infection, nausea, and vomiting, and rarely culminate in renal failure. Asymptomatic hematuria or repetitive urinary tract infections recalcitrant to apparently appropriate antibiotics should lead one to suspect a possible urinary stone. Calcifications within the parenchyma of the kidney, known as **nephrocalcinosis**, rarely cause symptoms, however, and usually are not amenable to traditional therapies appropriate for urinary stone disease (Figure 17–3). Nephrocalcinosis is frequently encountered with renal tubular acidosis and hyperparathyroidism. Nephrolithiasis and nephrocalcinosis frequently coexist.



▲ **Figure 17–3.** Retrograde pyelogram demonstrating multiple punctate calcifications within the renal parenchyma establishing the diagnosis of nephrocalcinosis. Renal pelvis and infundibula are free of calculi.

Most patients with nephrolithiasis, however, do not have obvious nephrocalcinosis as appreciated with conventional clinical radiographs. Ex vivo evaluation of human renal papilla, however, reveal clinically unappreciated proximal papillary biomineralization.

Nephrocalcinosis may result from a variety of pathologic states. Ectatic collecting tubules, as seen with medullary sponge kidney, are common; this is frequently a bilateral process. Theoretically, obstructed collecting ducts may be a source of chronic flank pain. Increased calcium absorption from the small bowel is common with sarcoidosis, milk-alkali syndrome, hyperparathyroidism, and excessive vitamin D intake. Disease processes resulting in bony destruction, including hyperparathyroidism, osteolytic lesions, and multiple myeloma, are a third mechanism. Finally, dystrophic calcifications forming on necrotic tissue may develop after a renal insult.

1. Absorptive hypercalciuric nephrolithiasis—Normal calcium intake averages approximately 900–1000 mg/day. Approximately one-third is absorbed by the small bowel, and of that portion, approximately 150–200 mg is obligatorily excreted in the urine. A large reservoir of calcium remains in the bone. Most dietary calcium is excreted in the stool. Absorptive hypercalciuria is secondary to increased calcium absorption from the small bowel, predominantly from the jejunum. This results in an increased load of calcium filtered from the glomerulus. The result is suppression of parathyroid hormone, leading to decreased tubular reabsorption of calcium, culminating in hypercalciuria (>4 mg/kg). This physiologic cascade is in response to the primary defect, an increased absorption of calcium from the small bowel.

Absorptive hypercalciuria traditionally has been subdivided into three types. Type I absorptive hypercalciuria is independent of diet and represents 15% of all calcareous calculi. There is an elevated urinary calcium level (>150–200 mg/24 hour) even during a calcium-restricted diet. Cellulose phosphate is an effective nonabsorbable exchange resin. This effectively binds the calcium in the gut, preventing bowel absorption. Cellulose phosphate has no impact on the calcium transport defect. Urinary calcium excretion returns to normal values with therapy.

Cellulose phosphate must be taken with meals to be available when calcium is ingested. A typical dose is 10–15 g orally in three divided doses and is well tolerated. This therapy is relatively contraindicated in postmenopausal women and in children during their active growth cycles. Inappropriate use may lead to a negative calcium balance and a secondary hyperparathyroid state. As with all stone formers, long-term follow-up is required. Cellulose phosphate may bind other cations besides calcium, including magnesium. Secondary hyperoxaluria may develop as a result of decreased calcium in the gut. Cellulose phosphate, however, is rarely utilized today as fasting and calcium load testing of urine is not routinely performed. See the section on hyperoxaluria for a more detailed discussion.

Hydrochlorothiazides are an alternative, more common treatment for type I absorptive hypercalciuria. Initially, there is a reduction in renal excretion of calcium. The increased absorbed calcium is likely deposited in bone. Eventually, the bone reservoir reaches its capacity and the drug becomes less effective. Hydrochlorothiazides have limited long-term efficacy (approximately 3–5 years). These drugs have no effect on the defective bowel transport systems. Hydrochlorothiazides may be alternated with cellulose phosphate as an effective treatment regimen.

Type II absorptive hypercalciuria is diet-dependent. There is no specific medical therapy. Calcium excretion returns to normal on a calcium-restricted diet. These are the rare patients that should limit their calcium intake to 400–600 mg/day. Type II absorptive hypercalciuria is not as severe as type I. Unfortunately, this diagnosis has led many patients and physicians to recommend limiting dietary and supplemental calcium intake. In fact, increased dietary intake of calcium generally results in decreased stone recurrence.

Type III absorptive hypercalciuria is secondary to a phosphate renal leak and accounts for 5% of all urinary calculi. Decreased serum phosphate leads to an increase in 1,25-dihydroxyvitamin D synthesis. The physiologic cascade culminates in an increased absorption of phosphate, and calcium, from the small bowel and an increased renal excretion of calcium—hence its classification as absorptive hypercalciuria. Successful treatment replaces bioavailable phosphate. Orthophosphate (Neutra-Phos, available over the counter) inhibits vitamin D synthesis and is best taken as 250 mg 3 or 4 times daily. It is best taken after meals and before bedtime. Orthophosphates do not alter intestinal calcium absorption.

2. Resorptive hypercalciuric nephrolithiasis—A subset (<10%) of patients with clinically obvious primary hyperparathyroidism present with nephrolithiasis. This group represents less than 5% of all patients with urinary stones and are more commonly seen in women. Patients with calcium phosphate stones, women with recurrent calcium stones, and those with both nephrocalcinosis and nephrolithiasis should be suspected of having hyperparathyroidism. Hypercalcemia and an elevated serum parathyroid level are the most consistent signs of hyperparathyroidism.

Parathyroid hormone results in a cascade of events starting with an increase in urinary phosphorus and a decrease in plasma phosphorus, followed by an increase in plasma calcium and a decrease in urinary calcium. Its actions on the kidney and on the bone are independent of each other. Ultimately, renal damage is secondary to the hypercalcemia. It limits the concentrating ability of the kidney and impairs the kidney's ability to acidify urine. Surgical removal of the offending parathyroid adenoma is the most effective way of treating this disease. However, up to 10% of these patients will develop new urinary stones after successful surgery, most commonly seen in men. Attempts at long-term medical management are challenging.

3. Renal hypercalciuric nephrolithiasis—Hypercalciuria of renal origin is due to an intrinsic renal tubular defect in calcium excretion. This creates a physiologically vicious cycle. Excessive urinary calcium excretion results in a relative decrease in serum calcium, which leads to a secondarily increased parathyroid hormone level that mobilizes calcium from the bone and increases calcium absorption from the gut. This step completes the pathologic cycle by delivering increased levels of calcium back to the kidney, whereby the renal tubules excrete large amounts of calcium. These patients have an elevated fasting urinary calcium level, normal serum calcium level, and a secondarily elevated parathyroid hormone level.

Renal hypercalciuria is effectively treated with hydrochlorothiazide. Unlike their role in type I absorptive hypercalciuria, in this setting hydrochlorothiazide has a durable long-term effect. As a diuretic, hydrochlorothiazide decreases the circulating blood volume and subsequently stimulates proximal tubular absorption of calcium as well as other constituents. It also increases reabsorption at the distal tubule. Both mechanisms correct the secondary hyperparathyroid state.

Hypercalciuric states may result in elevated parathyroid levels. To help differentiate primary hyperparathyroidism from secondary hyperparathyroidism in patients with urinary stone disease, one can prescribe a hydrochlorothiazide challenge (50 mg twice daily for 7–10 days). Patients with secondary hyperparathyroidism will have a return to normal serum parathyroid levels, while those with primary hyperparathyroidism will continue to have elevated serum values.

4. Hyperuricosuric calcium nephrolithiasis—Hyperuricosuric calcium nephrolithiasis is due to either an excessive dietary intake of purines or an increase in endogenous uric acid production. In both situations, there is an increase in urinary monosodium urates. Monosodium urates absorb and adsorb urinary stone inhibitors and facilitate heterogeneous nucleation.

Patients have elevated urinary uric acid levels (>600 mg/24 hour in women and >750 mg/24 hour in men) and consistently have a urinary pH of >5.5. The urinary pH helps differentiate hyperuricosuric calcium from hyperuricosuric uric acid stone formation.

Patients with excessive purine oral intake can be successfully treated by changing them to a low-purine diet. Those with excessive endogenous uric acid production can be treated with allopurinol. Allopurinol is a xanthine oxidase inhibitor and reduces uric acid synthesis and renal excretion of uric acid. It also inhibits uric acid–calcium oxalate crystallization. Allopurinol has many potential side effects, including a variety of skin rashes and, rarely, liver toxicity. Potassium citrate is an alternative treatment, especially when associated with hypocitraturia.

5. Hyperoxaluric calcium nephrolithiasis—Hyperoxaluric calcium nephrolithiasis is secondary to increased urinary oxalate levels (>40 mg/24 hour). It is frequently found in patients with inflammatory bowel disease or other chronic diarrheal states that result in severe dehydration. It can be associated with excessive oxalate intake, as seen in poisoning with ethylene glycol or endogenous overproduction.

Chronic diarrheal states alter oxalate metabolism. Malabsorption leads to increased luminal fat and bile salts. Intraluminal gut calcium readily and preferentially binds to fat and bile, resulting in a saponification process. The intraluminal gut calcium that normally would have bound to oxalate is thus decreased. The unbound oxalate is readily absorbed and is unaffected by the usual metabolic inhibitors of energy-dependent pumps. Bile salts may increase the passive bowel absorption of oxalate. A small increase in oxalate absorption and subsequent urinary excretion dramatically increases the formation product of calcium oxalate. This increases the potential for heterogeneous nucleation and crystal growth in this metastable environment. All patients with increased urinary excretion of oxalate do not necessarily form calcium oxalate calculi; other factors must be contributory.

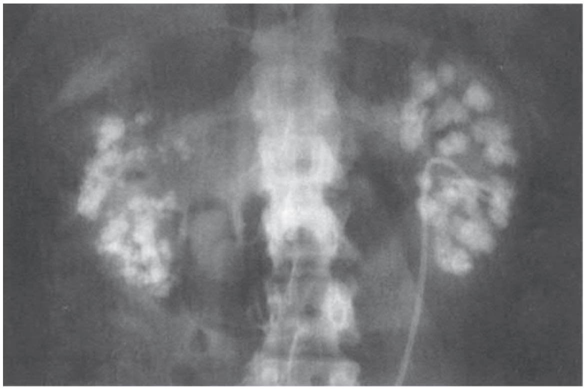
Enteric hyperoxaluric calcium nephrolithiasis is successfully treated with oral calcium supplementation. The calcium binds to the intraluminal oxalate and thus limits its absorption. It must be given with meals when the oxalate is present. Other oral cations are effective binders including magnesium supplements. An alternative therapy includes a diet limited to medium-chain fatty acids and triglycerides; however, it is poorly tolerated by patients. Equally difficult is an attempt to alter oxalate intake. Unless large amounts of specific oxalate-rich foods can be excluded, an alternative diet may result in *increased* oxalate levels.

Primary hyperoxaluria is a rare hereditary disease. It is associated with calcium oxalate renal calculi, nephrocalcinosis, and other distant deposits of oxalate, culminating in progressive renal failure and eventual death. Type I is associated with an enzyme deficiency of alanine-glyoxylate:aminotransferase (AGT) in the liver, resulting in elevated urinary levels of glycolic acid and oxalic acid. Type II (a deficiency in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) has increased excretory levels of L-glyceric acid rather than elevated levels of glycolic acid. This ultimately results in the accumulation of hydroxypyruvate, which is eventually converted to oxalate. A more recent type III primary hyperoxaluria recently has been described. In all three types vitamin B_6 appears to be important and as such is used as an adjunct to therapy. Oxalate crystal deposits develop rapidly in transplanted kidneys. Thus, combined liver and renal transplantation has cured this previously fatal rare disease.

6. Hypocitraturic calcium nephrolithiasis—Citrate is an important inhibitor of urinary stone disease. Increased metabolic demands on the mitochondria of proximal renal tubular cells decrease the excretion of citrate. Such conditions include intracellular metabolic acidosis, hypokalemia (as with thiazide therapy), fasting, hypomagnesemia, androgens, gluconeogenesis, and an acid-ash diet. Citrate may be consumed in the urine by bacteria during a urinary tract infection. The cause of hypocitraturia may be unknown in some cases. In contrast, alkalosis, alkaline-ash diet, estrogen, and vitamin D increase urinary citrate levels.

Citrate acts in solution and complexes with calcium. This decreases the ionic calcium concentration and thus the activity product. Citrate decreases agglomeration, spontaneous nucleation, and crystal growth of calcium oxalate. It also decreases calcium oxalate calculi by decreasing monosodium urates that can absorb inhibitors and facilitate heterogeneous nucleation.

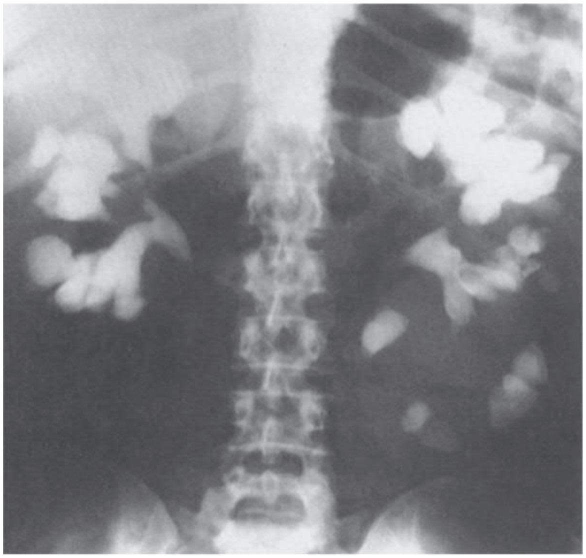
Hypocitraturic (<450 mg/24 hours) calcium nephrolithiasis is associated commonly with renal tubular acidosis type I (distal tubule) (Figure 17–4), thiazide therapy (accompanied by potassium wastage), and chronic diarrhea. Treatment is successful with potassium citrate supplementation. Routine dosage is 20–30 mEq 2 or 3 times daily (tablet, crystal, or liquid preparation) and is usually well tolerated. Six to eight glasses of lemonade can increase urinary citrate excretion by approximately 150 mg/24 hours and thus either limit or eliminate the need for pharmacologic citrate supplementation.



▲ **Figure 17–4.** Scout abdominal radiograph demonstrating bilateral, multiple renal calculi in a patient with renal tubular acidosis, type I.

B. Noncalcium Calculi

1. Struvite—Struvite stones are composed of magnesium, ammonium, and phosphate (MAP). They are found most commonly in women and may recur rapidly. They frequently present as renal staghorn configured calculi (branched with stones occupying the renal pelvis and at least to renal infundibuli) and rarely present as obstructing ureteral stones except after surgical intervention (Figure 17–5). Struvite stones are infection stones associated with urea-splitting organisms, including *Proteus*, *Pseudomonas*, *Providencia*, *Klebsiella*, *Staphylococci*, and *Mycoplasma.* The high ammonium concentration derived from the urea-splitting organisms results in an alkaline urinary pH. The urinary pH of a patient with a MAP stone rarely is <7.2 (normal urinary pH is 5.85). It is only at this elevated urinary pH (>7.19) that MAP crystals precipitate. MAP crystals are soluble in the normal urinary pH range of 5–7. Preoperative bladder cultures do not necessarily reflect the bacteriologic composition found in calculi. Foreign bodies and neurogenic bladders may predispose patients to urinary



▲ **Figure 17–5.** Scout abdominal radiograph demonstrating large bilateral struvite staghorn calculi. Patient was treated for many years with numerous antibiotics for recurrent urinary tract infections. Only after this radiograph were calculi identified and removed and the infections resolved.

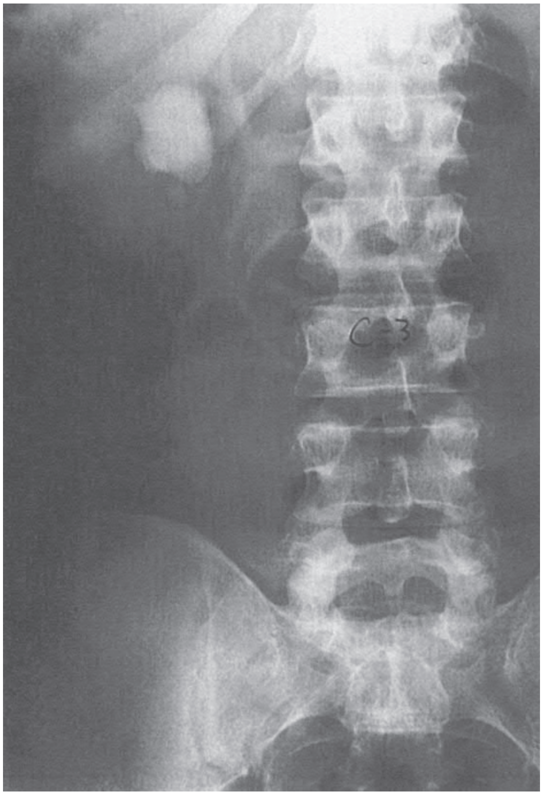
infections and subsequent struvite stone formation. Massive diuresis does not prevent struvite calculi. Women with recurrent non–*Escherichia coli* urinary infections despite apparently appropriate antibiotic therapy should be evaluated for struvite calculi with a conventional kidney–ureter–bladder (KUB) radiograph or renal ultrasound, or both. It is impossible to sterilize such calculi with antibiotics. Culture-specific antibiotics can reduce urease levels and help reduce stone recurrence. Stone removal is therapeutic.

Long-term management is optimized with the removal of all foreign bodies, including catheters of all varieties. A short ileal loop urinary diversion helps decrease the risk of stones in those with supravesical urinary diversion. All stone fragments should be removed with or without the aid of follow-up irrigations. Hemiacidrin (Renacidin) irrigations should be used with caution if at all. Rapid magnesium toxicity can result in death even with a low-pressure irrigation setup (<20 cm water pressure) and negative daily urine cultures. Acetohydroxamic acid inhibits the action of bacterial urease, thereby reducing the urinary pH and decreasing the likelihood of precipitation. Most patients have a difficult time tolerating this medication.

2. Uric acid—Uric acid stones constitute <5% of all urinary calculi and are usually found in men. Patients with gout, myeloproliferative diseases, or rapid weight loss and those treated for malignant conditions with cytotoxic drugs have an increased incidence of uric acid lithiasis. Most patients with uric acid calculi, however, do not have hyperuricemia. Elevated urinary uric acid levels are frequently due to dehydration and excessive purine intake. Patients present with a urinary pH consistently <5.5, in contrast to patients with hyperuricosuric calcium nephrolithiasis, who have a urinary pH of >5.5. As the urinary pH increases above the dissociation constant pK_a of 5.75, it dissociates into a relatively soluble urate ion. Treatment is centered on maintaining a urine volume >2 L/day and a urinary pH of >6.0. Reducing dietary purines or the administration of allopurinol also helps reduce uric acid excretion. Alkalinization, however, is the mainstay of therapy (with oral sodium bicarbonate, potassium bicarbonate, potassium citrate, or intravenous 1/6 normal sodium lactate) and may dissolve calculi (the rate of dissolution is dependent on the stone surface area). Stone fragments after lithotripsy have a dramatically increased surface area compared with intact stones and thus will dissolve more rapidly. Dissolution proceeds at approximately 1 cm of stone (as seen on KUB) per month, with compliant alkalinization.

3. Cystine—Cystine lithiasis is secondary to an inborn error of metabolism resulting in abnormal intestinal (small-bowel) mucosal absorption and renal tubular absorption of dibasic amino acids, including cystine, ornithine, lysine, and arginine. The genetic defects associated with cystinuria have now been mapped to chromosome 2p.16 and more recently to 19q13.1. Cystine lithiasis is the only clinical manifestation of this defect. Classic cystinuria is inherited in an autosomal recessive fashion. Homozygous expression has a prevalence of 1:20,000, while the heterozygous expression is 1:2000. It represents 1–2% of all urinary stones, with a peak incidence in the second or third decade. Homozygous cystinurics excrete more than 250 mg/day, resulting in constant supersaturation. Heterozygous patients usually excrete 100–150 mg/day. Unaffected patients typically excrete <40 mg/day. Approximately 400 mg/L of cystine can remain in solution at a urinary pH of 7.0. As the urinary pH increases above 7.0, the amount of soluble cystine increases exponentially.

The solubility of cystine is pH-dependent, with a p*K* of approximately 8.1. There is no difference in the solubility curves in normal versus patients with cystinuria. There is no known inhibitor for cystine calculi, and cystine stone formation is completely dependent on excessive cystine excretion. Cystine stones are frequently associated with calcium calculi and their related metabolic abnormalities. They may present as single, multiple, or staghorn configured stones. The diagnosis is suspected in patients with a family history of urinary stones and the radiographic appearance of a faintly opaque, ground-glass, smooth-edged stone (Figure 17–6). Urinalysis



▲ **Figure 17–6.** Scout radiograph demonstrating a right cystine calculus. Note ground-glass appearance with smooth edges.

frequently reveals hexagonal crystals. The stones have an amber color. Stone analysis confirms the diagnosis. Quantitative urinary cystine evaluation helps confirm the diagnosis and differentiate heterozygous from homozygous states. It is also important to help titrate medical therapy.

Medical therapy includes high fluid intake (>3 L/day, day and night) and urinary alkalinization. Patients should monitor their pH with Nitrazine indicator paper and keep their pH values above 7.5. It is difficult or impossible to maintain levels of >8.0. A low-methionine (precursor to cystine) diet has limited impact, as most of the cystine is endogenous and most of the ingested methionine is incorporated into protein. Glutamine, ascorbic acid, and captopril are effective in some patients. Penicillamine can reduce urinary cystine levels. It complexes with the amino acid, and this complex is dramatically more soluble. Treatment should be titrated with quantitative urinary cystine values. Many patients tolerate penicillamine poorly, reporting skin rashes (discrete or confluent macules with occasional itching), loss of taste, nausea, vomiting, and anorexia. Penicillamine may inhibit pyridoxine, which should be supplemented during treatment (50 mg/day). Mercaptopropionylglycine (Thiola), 300–1200 mg in divided doses, with initial dosing matched with total quantitative cystine excretion (milligram per milligram), forms a soluble complex with cystine and can reduce stone formation, and is the most commonly used sulfide-binding drug. Side effects and frequent dosing, however, decrease patient compliance. Recent experimental data have shown the potential impact of α-lipoic acid. Ongoing clinical trials are underway to assess whether these dramatic findings in a mouse model can be duplicated in our patients.

Surgical treatment is similar to that for other stones except that most stones are recalcitrant to extracorporeal shockwave lithotripsy (SWL). One should have a low threshold to proceed with percutaneous stone extraction in symptomatic patients. Despite optimum medical therapy, a high stone recurrence rate frequently frustrates both patient and physician. Minimally invasive techniques and optimum medical therapy are paramount.

4. Xanthine—Xanthine stones are secondary to a congenital deficiency of xanthine dehydrogenase. This enzyme normally catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid. It is of interest that allopurinol, used to treat hyperuricosuric calcium nephrolithiasis and uric acid lithiasis, produces iatrogenic xanthinuria. Blood and urine levels of uric acid are lowered, and hypoxanthine and xanthine levels are increased; however, there are no case reports of xanthine stone formation resulting from allopurinol treatment. It is unlikely that allopurinol completely inhibits xanthine dehydrogenase. Urinary stones develop in approximately 25% of patients with this enzymatic deficiency. The stones are radiolucent and are tannish yellow in color. Treatment should be directed by symptoms and evidence of renal obstruction. High fluid intake and urinary alkalinization are required for prophylaxis. If stones recur, a trial of allopurinol and a purine-restricted diet is appropriate.

5. Indinavir—Protease inhibitors are a popular and effective treatment in patients with acquired immunodeficiency syndrome. Indinavir is the most common protease inhibitor that results in radiolucent stones in up to 6% of patients who are prescribed this medication. Indinavir calculi are the only urinary stones to be radiolucent on noncontrast CT scans. They may be associated with calcium components and in these situations will be visible on noncontrast CT images. Temporary cessation of the medication with intravenous hydration frequently allows these stones to pass. The stones are tannish red and usually fall apart during basket extraction.

6. Rare—Silicate stones are very rare and are usually associated with long-term use of antacids containing silica. Surgical treatment is similar to that of other calculi. Triamterene stones are radiolucent and have been identified with an increased frequency. They are associated with antihypertensive medications containing triamterene, such as Dyazide. Discontinuing the medication eliminates stone recurrences. Other medications that may become stone constituents include glafenine and antrafenine.

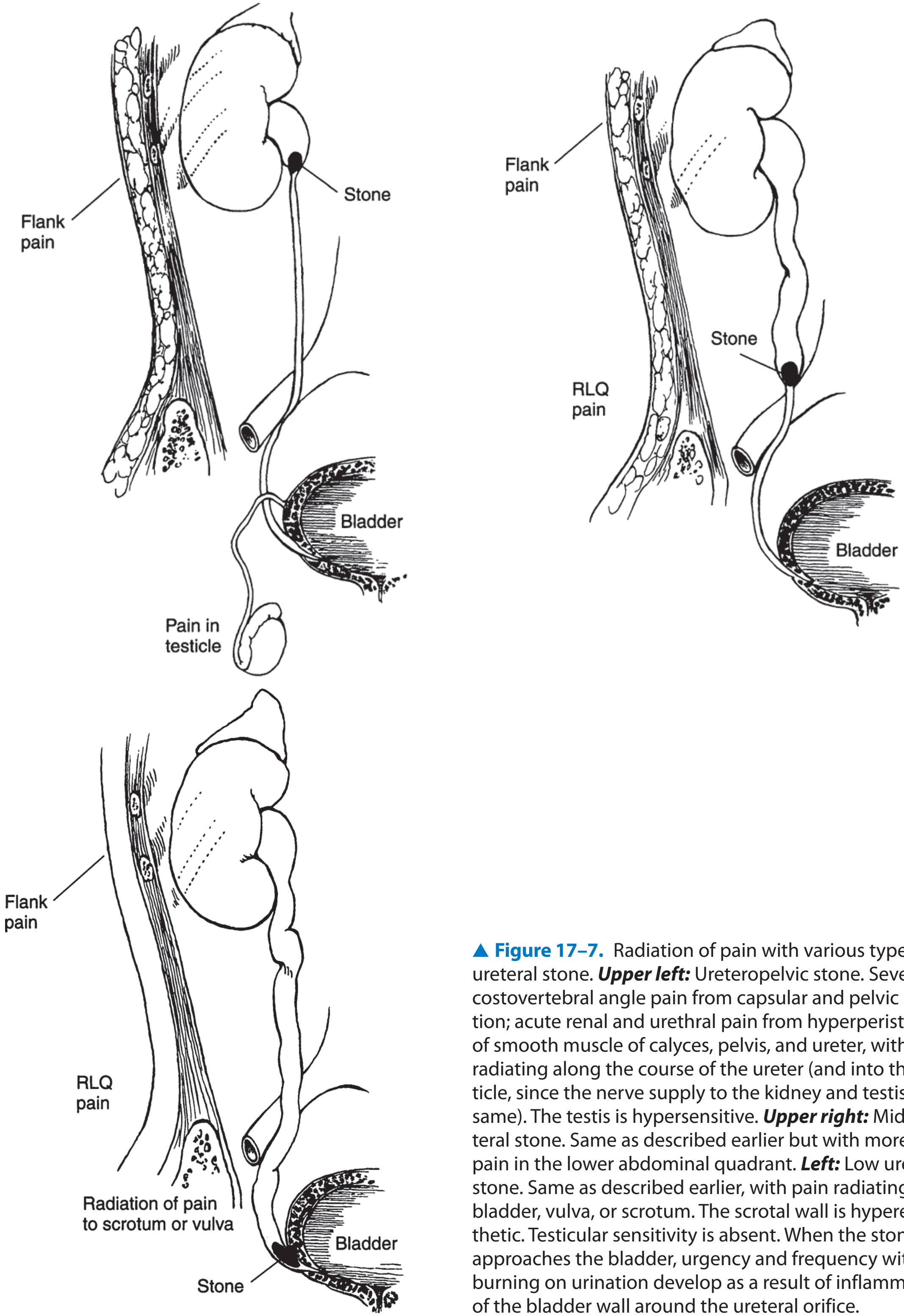
Rarely, patients arrive at an emergency room at an odd hour feigning signs and symptoms of passing a urinary stone in hopes of obtaining pain medications. They may add blood to their urine and give a believable story of a severe allergy to intravenous contrast medium. Occasionally, patients present a fake urinary stone, with specks of paint or other obvious curiosities. Such patients have Munchausen syndrome, and the diagnosis is difficult and made by exclusion.

Symptoms and Signs at Presentation

Upper tract urinary stones frequently cause pain when passing down the ureter. The character of the pain depends on the location. Calculi small enough to venture down the ureter usually have difficulty passing through the ureteropelvic junction, or entering the bladder at the ureterovesical junction (Figure 17–7). More than 60% of patients presenting with ureteral colic will have stones within 3 cm of the ureterovesical junction.

A. Pain

Renal colic and noncolicky renal pain are the two types of pain originating from the kidney. Renal colic usually is caused by stretching of the collecting system or ureter, whereas noncolicky renal pain is caused by distention of the renal capsule. These symptoms may overlap, making a clinical differentiation difficult or impossible. Urinary obstruction is the main mechanism responsible for renal colic. This may be mimicked by the pain that a patient experiences when a retrograde ureteropyelogram is performed under local anesthesia, with excessive pressure resulting in overdistention of



▲ **Figure 17–7.** Radiation of pain with various types of ureteral stone. ***Upper left:*** Ureteropelvic stone. Severe costovertebral angle pain from capsular and pelvic distention; acute renal and urethral pain from hyperperistalsis of smooth muscle of calyces, pelvis, and ureter, with pain radiating along the course of the ureter (and into the testicle, since the nerve supply to the kidney and testis is the same). The testis is hypersensitive. ***Upper right:*** Midureteral stone. Same as described earlier but with more pain in the lower abdominal quadrant. ***Left:*** Low ureteral stone. Same as described earlier, with pain radiating into bladder, vulva, or scrotum. The scrotal wall is hyperesthetic. Testicular sensitivity is absent. When the stone approaches the bladder, urgency and frequency with burning on urination develop as a result of inflammation of the bladder wall around the ureteral orifice.

the collecting system. This pain is due to a direct increase in intraluminal pressure, stretching nerve endings.

Renal colic does not always wax and wane or come in waves like intestinal or biliary colic but may be relatively constant. Renal colic implies an intraluminal origin. Patients with renal calculi have pain primarily due to urinary obstruction.

Local mechanisms such as inflammation, edema, hyperperistalsis, and mucosal irritation may contribute to the perception of pain in patients with renal calculi. In the ureter, however, local pain is referred to the distribution of the ilioinguinal nerve and the genital branch of the genitofemoral nerve, whereas pain from obstruction is referred to the same areas as for collecting system calculi (flank and costovertebral angle), thereby allowing discrimination.

Most urinary stones present with the acute onset of pain due to acute obstruction and distention of the upper urinary tract. The severity and location of the pain can vary from patient to patient relative to stone size, stone location, degree of obstruction, acuity of obstruction, and variation in individual anatomy (eg, intrarenal vs extrarenal pelvis). The stone burden does not correlate with the severity of the symptoms. Small ureteral stones frequently present with severe pain, whereas large staghorn configured calculi may present with a dull ache or flank discomfort.

The pain frequently is abrupt in onset and severe and may awaken a patient from sleep. The severity of the pain is worsened by the unexpected nature of its onset. Patients frequently move constantly into unusual positions while attempting to relieve the pain. This movement contrasts with the lack of movement of someone with peritoneal signs; such a patient lies in a stationary position.

The symptoms of acute renal colic depend on the location of the calculus; several regions may be involved: renal calyx, renal pelvis, upper ureter and midureter, and distal ureter. An orderly progression of symptoms as a stone moves down the urinary tract is the exception.

1. Renal calyx—Stones or other objects in calyces or caliceal diverticula may cause obstruction and renal colic. In general, nonobstructing stones cause pain only periodically, owing to intermittent obstruction. The pain is a deep, dull ache in the flank or back that can vary in intensity from severe to mild. The pain may be exacerbated after consumption of large amounts of fluid. Radiographic imaging may not reveal evidence of obstruction despite the patient's complaints of intermittent symptoms. It remains unclear how much of this pain is related to local mucosal irritation with activation of chemoreceptors. The presence of infection or inflammation in the calyx or diverticulum (eg, milk of calcium) in addition to obstruction may contribute to pain perception. Caliceal calculi occasionally result in spontaneous perforation with urinoma, fistula, or abscess formation.

Caliceal calculi are frequently small and numerous and appear to be able to pass spontaneously. Long-term retention against the flow of urine and against the forces of gravity and antegrade peristalsis suggests a significant element of obstruction. Effective long-term treatment requires stone extraction and elimination of the obstructive component.

Pain relief has been reported in many patients following SWL for small symptomatic caliceal calculi. Thus, if a patient continues to complain of pain in the face of a small caliceal calculus, SWL treatment may be justified for both diagnosis and treatment. Percutaneous, retrograde, and laparoscopic techniques have been successful in the management of calculi in calyces or caliceal diverticula.

2. Renal pelvis—Stones in the renal pelvis >1 cm in diameter commonly obstruct the ureteropelvic junction, generally causing severe pain in the costovertebral angle, just lateral to the sacrospinalis muscle and just below the 12th rib. This pain may vary from dull to excruciatingly sharp and is usually constant, boring, and difficult to ignore. It often radiates to the flank and anteriorly to the upper ipsilateral abdominal quadrant. It may be confused with biliary colic or cholecystitis if on the right side and with gastritis, acute pancreatitis, or peptic ulcer disease if on the left, especially if the patient has associated anorexia, nausea, or emesis. Acquired or congenital ureteropelvic junction obstruction may cause a similar constellation of symptoms. Symptoms frequently occur on an intermittent basis following a drinking binge or consumption of large quantities of fluid.

Partial or complete staghorn configured calculi that are present in the renal pelvis are not necessarily obstructive. In the absence of obstruction, these patients often have surprisingly few symptoms such as flank or back pain. Recurrent urinary tract infections frequently culminate in radiographic evaluation with the discovery of a large calculus. If untreated, these "silent" staghorn calculi can often lead to significant morbidity, including renal deterioration, infectious complications, or both.

3. Upper ureter and midureter—Stones or other objects in the upper or mid ureter often cause severe, sharp back (costovertebral angle) or flank pain. The pain may be more severe and intermittent if the stone is progressing down the ureter and causing intermittent obstruction. A stone that becomes lodged at a specific site may cause less pain, especially if it is only partially obstructive. Stationary calculi that result in high-grade but constant obstruction may allow autoregulatory reflexes and pyelovenous and pyelolymphatic backflow to decompress the upper tract, with diminution in intraluminal pressure gradually easing the pain. Pain associated with ureteral calculi often projects to corresponding dermatomal and spinal nerve root innervation regions. The pain of upper ureteral stones thus radiates to the lumbar region and flank. Midureteral calculi tend to cause pain that radiates caudally and anteriorly toward the middle and lower abdomen in a curved, bandlike fashion. This band initially parallels the lower costal margin but deviates caudad toward the bony pelvis and inguinal ligament. The pain may mimic acute appendicitis if on the right or acute diverticulitis if on the left side, especially if concurrent gastrointestinal symptoms are present.

4. Distal ureter—Calculi in the lower ureter often cause pain that radiates to the groin or testicle in males and the labia majora in females. This referred pain is often generated from the ilioinguinal or genital branch of the genitofemoral nerves. Diagnosis may be confused with testicular torsion or epididymitis. Stones in the intramural ureter may mimic cystitis, urethritis, or prostatitis by causing suprapubic pain, urinary frequency and urgency, dysuria, stranguria, or gross hematuria. Bowel symptoms are not uncommon. In women, the diagnosis may be confused with menstrual pain, pelvic inflammatory disease, and ruptured or twisted ovarian cysts. Strictures of the distal ureter from radiation, operative injury, or previous endoscopic procedures can present with similar symptoms. This pain pattern is likely due to the similar innervation of the intramural ureter and bladder.

B. Hematuria

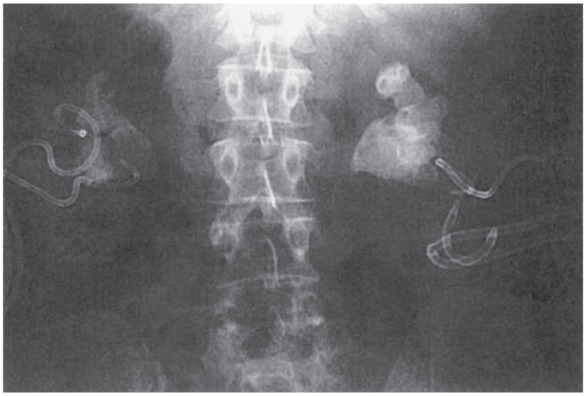
A complete urinalysis helps confirm the diagnosis of a urinary stone by assessing for hematuria and crystalluria and documenting urinary pH. Patients frequently admit to intermittent gross hematuria or occasional tea-colored urine (old blood). Most patients will have at least microhematuria. Rarely (in 10–15% of cases), complete ureteral obstruction presents without microhematuria.

C. Infection

Magnesium ammonium phosphate (struvite) stones are synonymous with infection stones. They are commonly associated with *Proteus*, *Pseudomonas*, *Providencia*, *Klebsiella*, and *Staphylococcus* infections. They are rarely, if ever, associated with *E. coli* infections. Calcium phosphate stones are the second variety of stones associated with infections. Calcium phosphate stones with a urine pH of <6.4 are frequently referred to as **brushite stones**, whereas infectious apatite stones have a urinary pH of >6.4. Rarely, matrix stones with minimal crystalline components are associated with urinary tract infections. All stones, however, may be associated with infections secondary to obstruction and stasis proximal to the offending calculus. Culture-directed antibiotics should be administered before elective intervention.

Infection may be a contributing factor to pain perception. Uropathogenic bacteria may alter ureteral peristalsis by the production of exotoxins and endotoxins. Local inflammation from infection can lead to chemoreceptor activation and perception of local pain with its corresponding referral pattern.

1. Pyonephrosis—Obstructive calculi may culminate in the development of pyonephrosis. Unlike pyelonephritis, pyonephrosis implies gross purulent urine in an obstructed collecting system. It is an extreme form of infected hydronephrosis. Presentation is variable and may range from asymptomatic bacteriuria to florid urosepsis. Bladder urine cultures may be negative. Radiographic investigations are frequently nondiagnostic. Renal ultrasonography may be misguiding because of the nonspecific and variable appearance of pyonephrosis. Renal urine aspiration is the only way to make the definitive diagnosis. If the condition is noted at the time of a percutaneous nephrolithotomy, the procedure should be aborted to allow for adequate percutaneous drainage and treatment with appropriate intravenous antibiotics (Figure 17–8). If unrecognized and untreated, pyonephrosis may develop into a renocutaneous fistula.



▲ **Figure 17–8.** Bilateral renal calculi seen on scout radiograph with numerous bilateral percutaneous nephrostomy tubes to drain severe bilateral pyonephrosis.

2. Xanthogranulomatous pyelonephritis—Xanthogranulomatous pyelonephritis is associated with upper tract obstruction and infection. Ultimately, this is a pathologic diagnosis with characteristic foamy macrophages. One-third of patients present with calculi; two-thirds present with flank pain, fever, and chills. One-half of patients present with persistent bacteriuria. Urinalysis usually shows numerous red and white cells. This condition is a common imitator of other pathologic states of the kidney. It usually presents in a unilateral fashion. Laparoscopic or open surgical procedures, such as a simple nephrectomy for minimal or renal function, can be challenging owing to marked and extensive reactive tissues.

D. Associated Fever

The association of urinary stones with fever is a relative medical emergency. Signs of clinical sepsis are variable and include fever, tachycardia, hypotension, and cutaneous vasodilation. Costovertebral angle tenderness may be marked with acute upper tract obstruction; however, it cannot be relied on to be present in instances of long-term obstruction. In such instances, a mass may be palpable, resulting from a grossly hydronephrotic kidney. Fever associated with urinary tract obstruction requires prompt decompression. This may be accomplished with a retrograde catheter (double-J, or an externalized variety to serve as a port for selective urine collections, injection of contrast material, or both). If retrograde manipulations are unsuccessful, insertion of a percutaneous nephrostomy tube is required.

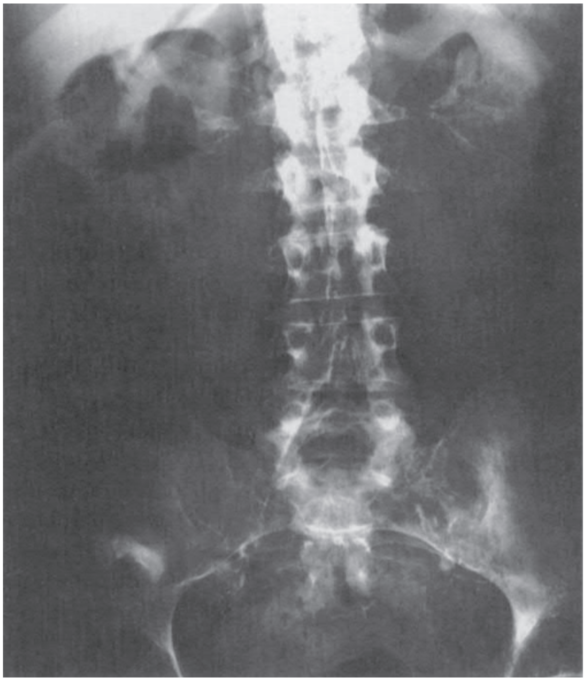
E. Nausea and Vomiting

Upper tract obstruction is frequently associated with nausea and vomiting. Intravenous fluids are required to restore a euvolemic state. Intravenous fluids should not be used to force a diuresis while attempting to push a ureteral stone down the ureter. Effective ureteral peristalsis requires coaptation of the ureteral walls and is most effective in a euvolemic state.

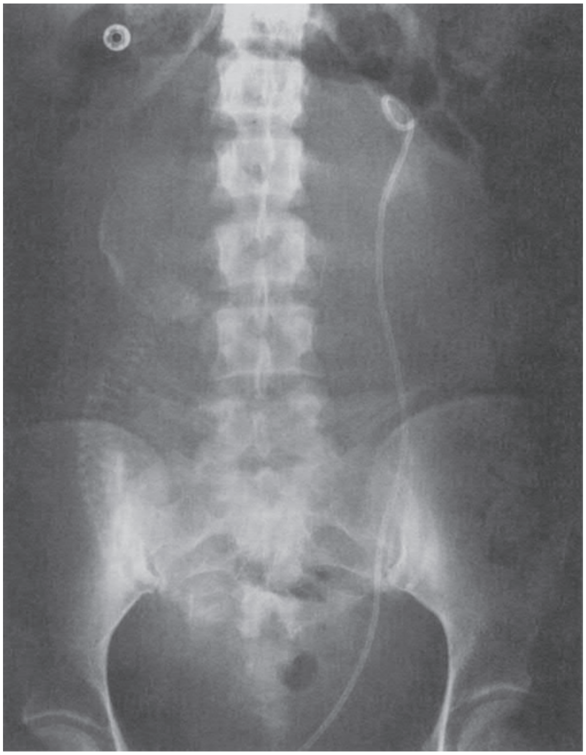
▶ Special Situations

A. Renal Transplantation

Urinary stones associated with renal transplantation are rare. Perirenal nerves are severed at the time of renal harvesting. Classic renal colic is not found in these patients. The patients usually are admitted with the presumptive diagnosis of graft rejection. Only after appropriate radiographic and ultrasonic evaluation is the correct diagnosis made (Figure 17–9).



▲ **Figure 17–9.** Scout abdominal radiograph demonstrating renal calculus in a renal transplant in the right iliac fossa. Note native renal vasculature with marked calcifications secondary to malignant diabetes mellitus.



▲ **Figure 17–10.** Scout radiograph demonstrating left renal calculus with double-J ureteral stent in place. Skeletal fetal structures can be appreciated in this pregnant patient.

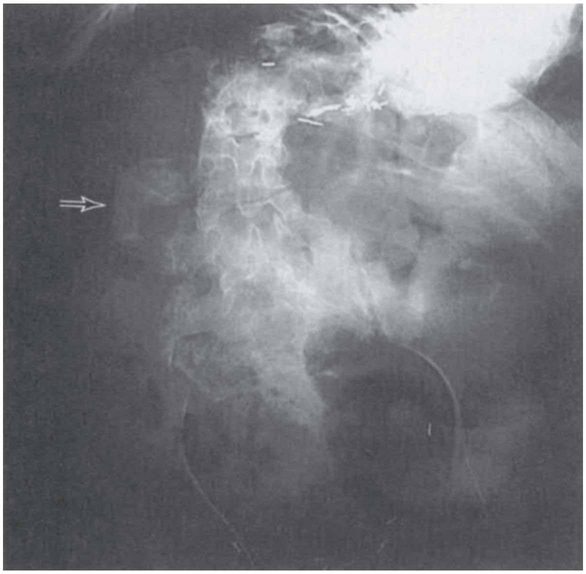
B. Pregnancy

Renal colic is the most common nonobstetric cause of acute abdominal pain during pregnancy (Figure 17–10). Despite marked hypercalciuria associated with pregnancy, calculi are relatively rare, with an incidence approximating 1:1500 pregnancies. Women with known urinary stone disease do not have an increased risk of stones during pregnancy. The increased filtered load of calcium, uric acid, and sodium from the 25–50% increase in glomerular filtration rate associated with pregnancy has been considered to be a responsible factor in stone development.

The fetus demands special considerations regarding the potential dangers of radiation exposure (especially during the first trimester), medications, anesthesia, and surgical intervention. About 90% of symptomatic calculi present during the second and third trimesters. Initial investigations can be undertaken with renal ultrasonography and limited abdominal x-rays with appropriate shielding. Treatment requires balancing the safety of the fetus with the health of the mother. Temporizing measures to relieve upper tract obstruction with a double-J ureteral stent or a percutaneous nephrostomy tube can be performed under local anesthesia. Double-J stents, however, can become encrusted in 4–6 weeks and as such need to be changed frequently prior to intervention after delivery.

C. Dysmorphia

Patients with severe skeletal dysmorphia that is either congenital (spina bifida, myelomeningocele, cerebral palsy) or acquired (arthritis, traumatic spinal cord injuries) and concurrent urinary calculi represent a unique clinical situation requiring special considerations (Figure 17–11). These skeletal abnormalities may preclude appropriate positioning for SWL or percutaneous approaches. Calculi on the concave side in a patient with severe scoliosis may eliminate percutaneous puncture access between the rib and the posterosuperior iliac spine. Retrograde manipulations may need to be performed with flexible endoscopes due to marked contractures, making conventional dorsal lithotomy positioning impossible. Many such patients have undergone supravesical urinary diversion so that retrograde access may be limited. Risks that need to be addressed include hypercalciuria associated with immobilization, relative dehydration due to patients' or attendants' attempts to reduce urinary output into external collecting devices, and the potential inability to drink without assistance. A full metabolic evaluation is even more important because these social and physical restrictions may be difficult or impossible to remedy.



▲ **Figure 17–11.** Scout abdominal radiograph demonstrating a right renal calculus (*arrow*) in a patient with severe kyphoscoliosis. Respiratory compromise limited patient positioning for surgery.

D. Obesity

Obesity is a major risk factor for the development of urinary calculi. Surgical bypass procedures can cause hyperoxaluria. Massive weight gain or loss also may precipitate stone development. Obesity limits diagnostic and treatment options. A large pannus may limit the physical examination and misguide incisions. Ultrasound examination is hindered by the attenuation of ultrasound beams. CT scan, magnetic resonance imaging, fluoroscopy tables, and lithotripters all have weight limitations, and patients weighing more than 300 lb may be unsuited for diagnosis and treatment with these resources. Standard lithotripters have focal lengths of <15 cm between the energy source and the F2 target, frequently making treatment of obese patients challenging. A large anterior pannus limits prone positioning on lithotripters. Standard Amplatz nephrostomy sheaths may not be long enough to enter the collecting system. Such sheaths may need to be advanced well below the skin, or specialized long sheaths with long nephroscopes may be required. A preplaced heavy suture eases removal of such sheaths. Positioning a patient in a modified supine fashion will allow for a combined percutaneous and retrograde access to the collecting system.

Risks of anesthesia are increased, and special high-pressure respirators may be required if patients are placed in a prone position for a percutaneous procedure. Careful positioning for open procedures helps to reduce the likelihood of crush injuries and associated rhabdomyolysis. These patients are at increased risk of anesthetic complications. Postoperative prophylaxis for thromboembolic complications should be considered.

E. Medullary Sponge Kidney

Medullary sponge kidney is a common condition characterized by tubular ectasia associated with parenchymal cysts and clefts that predispose to nephrolithiasis in 50% of affected patients. It is most often an asymptomatic condition; however, it may present with renal colic, hematuria, or urinary tract infection. It is a radiographic diagnosis. The condition can involve select papillae or, more frequently, can be global. A full metabolic evaluation helps direct appropriate medical therapy.

F. Renal Tubular Acidosis

There are three main types of renal tubular acidosis: types I, II, and IV. Type I is associated with renal calculi.

Patients with type I renal tubular acidosis present with persistent acidemia with a low serum bicarbonate value unexplained by hyperventilation or known renal failure. The diagnosis should be suspected in those with a known family history, severe hypocitraturia (<50 mg/24 hours), nephrocalcinosis, medullary sponge kidney, or a fasting urine pH of >6.0 in the absence of infection. Patients usually present with nephrolithiasis (calcium phosphate), nephrocalcinosis, or osteomalacia (or a combination). This disease can be acquired as an adult or inherited with an autosomal dominant pattern. The diagnosis is confirmed by assessing the patient's response to an acid load. This is frequently produced by a rapid oral ammonium chloride load (0.1 g/kg over 1 hour). The dose can be given before bedtime in the evening; the patient is instructed to fast until a second morning voided urine sample and a serum bicarbonate level are obtained. A normal person responds by eliminating the acid load in the urine, resulting in a urinary pH of <5.3. Those who do not respond in this fashion can be assumed to have type I renal tubular acidosis. In addition, the diagnosis should be challenged in those with normal citrate values. Treatment is centered on base replacement with potassium citrate or potassium bicarbonate solutions. Urinary citrate levels can be used to monitor effective treatment.

G. Associated Tumors

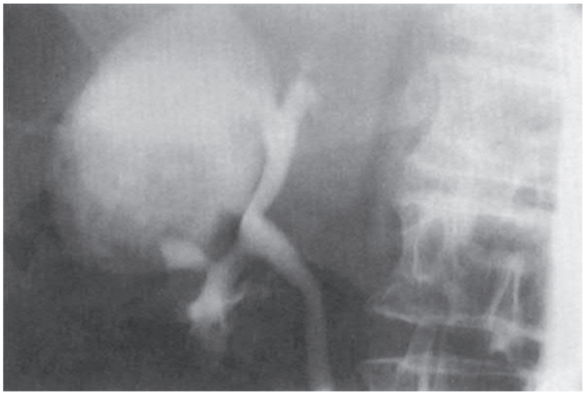
Squamous cell carcinoma of the upper urinary tract is uncommon but has been associated with calculi. Chronic irritation from calculi or infection may be contributory factors. Upper tract calculi may predispose patients to transitional cell carcinoma.

H. Pediatric Patients

Urinary calculi are unusual in children. A full and thorough metabolic evaluation should be undertaken. Unlike most issues with the pediatric age group, urinary stone disease has pathophysiologic cascades and treatment algorithms that are similar to those found in adults. Stone analysis is particularly helpful in directing these investigations. Children born prematurely and given furosemide while in the neonatal intensive care unit are at increased risk of developing urinary stone disease. Treatment may be limited by endoscope size. Preliminary data show no change in renal growth after SWL.

I. Caliceal Diverticula

Pyelocaliceal diverticula are cystic urine-containing eventrations of the upper tract lying within the renal parenchyma; they communicate through a narrow channel into the main collecting system (Figure 17–12). These diverticula occur in approximately 0.2–0.5% of the population and are congenital in origin; up to 40% are associated with calculi. Type I diverticula are the most common and are closely related to minor calyces. Type II diverticula have a direct communication with the renal pelvis and tend to be larger and symptomatic. Caliceal diverticuli are usually asymptomatic, but patients may complain of flank pain or recurrent urinary tract infections. Frequently, many small calculi, rather than a solitary stone, are found in these obstructed cavities. When intervention was required in the past, treatment was with nephrectomy, heminephrectomy, or open surgical unroofing. Less invasive means are used today. Communications with the collecting system are commonly pinpoint and may be difficult to locate through a retrograde approach. Retrograde access into superior pole diverticula has been successful. Surprisingly, treatment may be successful with SWL if stone fragments are small enough to pass uneventfully. More commonly, percutaneous access and, more recently, laparoscopic means are used with success. Dilation of the caliceal neck, direct cauterization or sclerosis of the caliceal epithelium, or direct cauterization and sclerosis of the caliceal epithelium can help reduce stone recurrence rates.



▲ **Figure 17–12.** Intravenous pyelogram demonstrating symptomatic right calyceal diverticula with numerous small calculi.

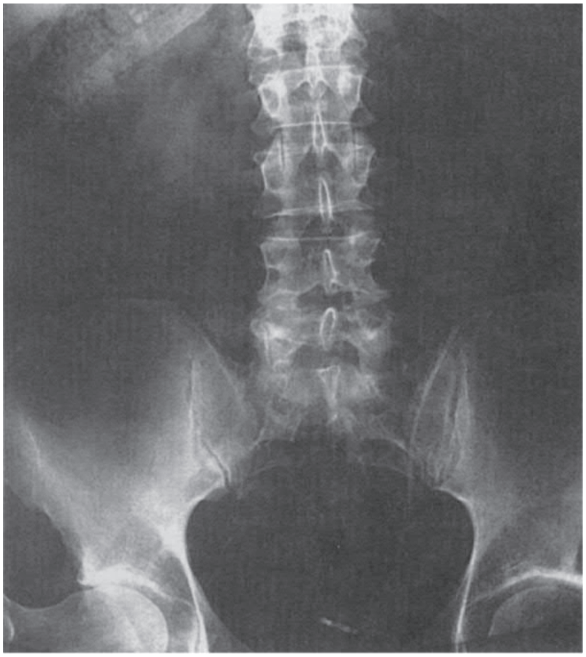
J. Renal Malformations

Anatomic renal variants such as ectopic kidneys, including the horseshoe and pelvic kidney, predispose to renal calculi due to impaired urinary drainage. Pain symptoms appear to be no different from those reported in patients with normally positioned kidneys. Radiographic diagnosis may be difficult due to the unexpected location of the ureters and kidneys (Figure 17–13). If calculi can be targeted with SWL, most stone fragments will pass surprisingly uneventfully. Large stone burdens should be approached percutaneously as in normally positioned kidneys. Severe outlet obstruction should be corrected with laparoscopic or open surgery, and concurrent calculi can be removed at the same setting. Aberrant vasculature should be appreciated before percutaneous, laparoscopic, and open procedures are undertaken.

▶ Evaluation

A. Differential Diagnosis

Urinary stones can mimic other retroperitoneal and peritoneal pathologic states. A full differential diagnosis of the acute abdomen should be made, including acute appendicitis; ectopic and unrecognized pregnancies; ovarian pathologic



▲ **Figure 17–13.** Scout abdominal radiograph demonstrating horseshoe kidney with lateral ureteral deviation and double-J ureteral stent. Extraosseous calcifications are left lower calyceal stones.

conditions including twisted ovarian cysts, diverticular disease, bowel obstruction, and biliary stones with and without obstruction; peptic ulcer disease; acute renal artery embolism; and abdominal aortic aneurysm—to mention only a few. Peritoneal signs should be sought during physical examination.

B. History

A proper evaluation requires a thorough medical history. The nature of the pain should be evaluated, including its onset; character; potential radiation; activities that exacerbate or ease the pain; associated nausea, vomiting, or gross hematuria; and a history of similar pain. Patients with previous stones frequently have had similar types of pain in the past, but not always.

C. Risk Factors

1. Crystalluria—Crystalluria is a risk factor for stones. Stone formers, especially those with calcium oxalate stones, frequently excrete more calcium oxalate crystals, and those crystals are larger than normal (>12 μm). The rate of stone formation is proportional to the percentage of large crystals and crystal aggregates. Crystal production is determined by the saturation of each salt and the urinary concentration of inhibitors and promoters. Urine samples should be fresh; they should be centrifuged and examined immediately for optimum results. Cystine crystals are hexagonal; struvite stones appear as coffin lids; brushite ($CaHPO_4$) stones are splinterlike and may aggregate with a spokelike center; calcium apatite—$(Ca)_5(PO_4)_3(OH)$—and uric acid crystals appear as amorphous powder because the crystals are so small; calcium oxalate dihydrate stones are bipyramids; and calcium oxalate monohydrate stones are small, biconcave ovals that may appear as a dumbbell. Cystine and struvite crystals are always abnormal and require further investigation. Other crystals are frequently found in normal urinalyses.

2. Socioeconomic factors—Renal stones are more common in affluent, industrialized countries. Immigrants from less industrialized nations gradually increase their stone incidence and eventually match that of the indigenous population. Use of soft water does not decrease the incidence of urinary stones.

3. Diet—Diet may have a significant impact on the incidence of urinary stones. As per capita income increases, the average diet changes, with an increase in saturated and unsaturated fatty acids; an increase in animal protein and sugar; and a decrease in dietary fiber, vegetable protein, and unrefined carbohydrates. A less energy-dense diet may decrease the incidence of stones. This fact has been documented during war years when diets containing minimal fat and protein resulted in a decreased incidence of stones. Vegetarians may have a decreased incidence of urinary stones. High sodium intake is associated with increased urinary sodium, calcium, and pH and a decreased excretion of citrate; this increases the likelihood of calcium salt crystallization because the urinary saturation of monosodium urate and calcium phosphate (brushite) is increased. Fluid intake and urine output may affect urinary stone disease. The average daily urinary output in stone formers is 1.6 L.

4. Occupation—Occupation can have an impact on the incidence of urinary stones. Physicians and other white-collar workers have an increased incidence of stones compared with manual laborers. This finding may be related to differences in diet but also may be related to physical activity; physical activity may agitate urine and dislodge crystal aggregates. Individuals exposed to high temperatures may develop higher concentrations of solutes owing to dehydration, which may have an impact on the incidence of stones.

5. Climate—Individuals living in hot climates are prone to dehydration, which results in an increased incidence of urinary stones, especially uric acid calculi. Although heat may cause a higher fluid intake, sweat loss results in lowered voided volumes. Hot climates usually expose people to more ultraviolet light, increasing vitamin D_3 production. Increased calcium and oxalate excretion have been correlated with increased exposure time to sunlight. This factor has more impact on light-skinned people and may help explain why African-Americans in the United States have a decreased stone incidence. Global warming may increase the incidence of urinary stone disease.

6. Family history—A family history of urinary stones is associated with an increased incidence of renal calculi. A patient with stones is twice as likely as a stone-free cohort to have at least one first-degree relative with renal stones (30% vs 15%). Those with a family history of stones have an increased incidence of multiple and early recurrences. Spouses of patients with calcium oxalate stones have an increased incidence of stones; this may be related to environmental or dietary factors. Large studies of identical twins have found that >50% of stones have a significant genetic component. A significant association between urinary stones and cardiovascular disease has been confirmed in many studies.

7. Medications—A thorough history of medications taken may provide valuable insight into the cause of urinary calculi. The antihypertensive medication triamterene is found as a component of several medications, including Dyazide, and has been associated with urinary calculi with increasing frequency. Long-term use of antacids containing silica has been associated with the development of silicate stones. Carbonic anhydrase inhibitors may be associated with urinary stone disease (10–20% incidence). The long-term effect of sodium- and calcium-containing medications on the development of renal calculi is not known. Protease inhibitors in immunocompromised patients are associated with radiolucent calculi.

D. Physical Examination

A detailed physical examination is an essential component of the evaluation of any patient suspected of having a urinary calculus. The patient presenting with acute renal colic typically is in severe pain, often attempting to find relief in multiple, frequently bizarre, positions. This fact helps differentiate patients with this condition from those with peritonitis, who are afraid to move. Systemic components of renal colic may be obvious, with tachycardia, sweating, and nausea often prominent. Costovertebral angle tenderness may be apparent. An abdominal mass may be palpable in patients with longstanding obstructive urinary calculi and severe hydronephrosis.

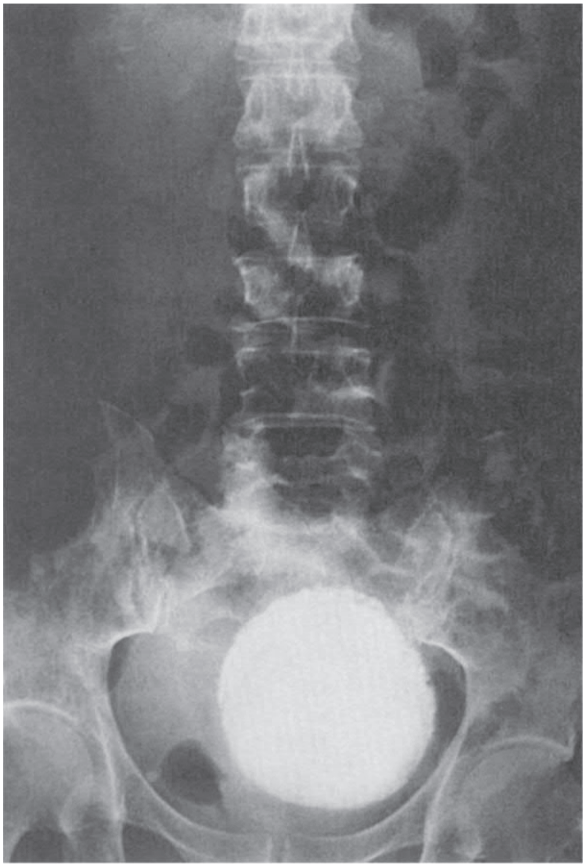
Fever, hypotension, and cutaneous vasodilation may be apparent in patients with urosepsis. In such instances, there is an urgent need for decompression of the obstructed urinary tract, massive intravenous fluid resuscitation, and intravenous antibiotics. Occasionally, intensive care support is needed.

A thorough abdominal examination should exclude other causes of abdominal pain. Abdominal tumors, abdominal aortic aneurysms, herniated lumbar disks, and pregnancy may mimic renal colic. Referred pain may be similar owing to common afferent neural pathways. Intestinal ileus may be associated with renal colic or other intraperitoneal or retroperitoneal processes. Bladder palpation should be performed because urinary retention may present with pain similar to that due to renal colic. Incarcerated inguinal hernias, epididymitis, orchitis, and female pelvic pathologic states may mimic urinary stone disease. A rectal examination helps exclude other pathologic conditions.

E. Radiologic Investigations

1. Computed tomography—Noncontrast spiral CT scans are now the imaging modality of choice in patients presenting with acute renal colic. It is rapid, is less expensive than an intravenous pyelogram (IVP), and is operator-independent. It images other peritoneal and retroperitoneal structures and helps when the diagnosis is uncertain. There is no need for intravenous contrast. Distal ureteral calculi can be confused with phleboliths. Prone positioning will help differentiate impacted ureterovesical junction calculi from stones that have already passed into the urinary bladder. Noncontrast images do not give anatomic details as seen on an IVP (eg, a bifid collecting system) that may be important in planning intervention. If intravenous contrast material is used during the study, a KUB film or three-dimensional reconstruction can give additional helpful information. Uric acid stones are visualized no differently from calcium oxalate stones. Matrix calculi have adequate amounts of calcium to be visualized easily by CT scan. Hounsfield unit measurement can help predict stone type and hardness. Hard calcium oxalate monohydrate stones, for example, frequently have a HU of >1000, whereas uric acid stones frequently have HU < 500. The increased use of CT scans has also increased the radiation exposure to stone patients, especially those with recurrent disease. Ultra-low-dose CT imaging is adequate to make a diagnosis of a urinary stone and has a radiation exposure similar to that of a KUB. A large prospective study found that patients presenting to emergency departments can be triaged appropriately with ultrasound studies without the need for formal CT imaging when used as the initial imaging modality. To help limit radiation exposure, CT scans should be used when the diagnosis is in doubt and should not be routinely utilized for diagnosis or surveillance.

2. Intravenous pyelography—An IVP can simultaneously document nephrolithiasis and upper tract anatomy. It is rarely used today with the widespread availability of CT scanners and ultrasound machines. Extraosseous calcifications on radiographs may be erroneously assumed to be urinary tract calculi (Figure 17–14). Oblique views easily differentiate gallstones from right renal calculi. Static hard-copy films can be interpreted by most clinicians. An inadequate bowel preparation, associated ileus and swallowed air, and lack of available technicians may result in a less than ideal study when obtained during acute renal colic. A delayed, planned IVP may result in a superior study.



▲ **Figure 17–14.** Scout abdominal radiograph demonstrating large extraosseous calcification that represents a uterine fibroid. This easily could be confused with a large bladder calculus.

Acute forniceal rupture is not uncommonly associated with a highly obstructive ureteral calculus (typically of a small distal ureteral stone). It may result in dramatic radiographs but is of no clinical significance, and no specific intervention is required. The rupture may be precipitated by the osmotic diuresis of the intravenous contrast agent.

3. Tomography—Renal tomography is useful to identify calculi in the kidney when oblique views are not helpful. It visualizes the kidney in a coronal plane at a set distance from the top of the x-ray table. Renal tomography may help identify poorly opacified calculi or stones difficult to appreciate secondary to overlying abdominal gas or morbid obesity when imaged with a traditional with a KUB.

4. KUB films and directed ultrasonography—A KUB film and renal ultrasound may be as effective as a CT scan in establishing a diagnosis. The ultrasound examination should be directed by notation of suspicious areas seen on a KUB film; it is, however, operator-dependent. The distal ureter is easily visualized through the acoustic window of a full bladder. Ultrasound imaging by a trained emergency physician, or by a radiologist appears just as useful when compared to CT imaging for the acute diagnosis of urinary stones.

5. Retrograde pyelography—Retrograde pyelography occasionally is required to delineate upper tract anatomy and localize small or radiolucent offending calculi. Bulb ureterograms frequently leak contrast material back into the bladder, resulting in a suboptimal study. Advancing an angiographic exchange catheter with or without the aid of a guidewire 3–4 cm into the ureter is an alternative technique. Intermittent fluoroscopic images direct appropriate injection volumes and help reduce the likelihood of pyelolymphatic, pyelosinus, and pyelovenous reflux.

6. Magnetic resonance imaging—Magnetic resonance imaging is a poor study to document urinary stone disease.

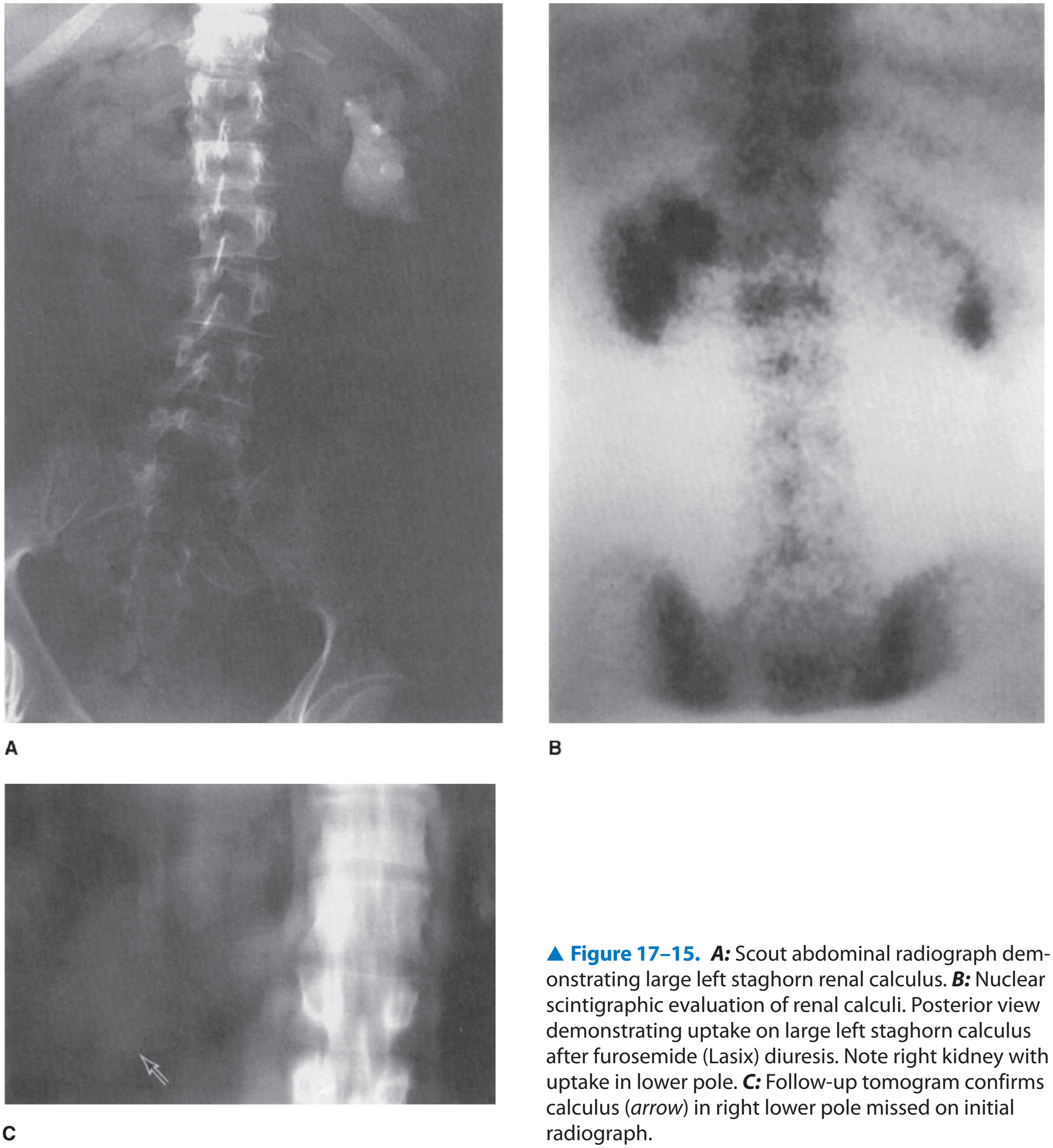
7. Nuclear scintigraphy—Nuclear scintigraphic imaging of stones has recently been appreciated. Bisphosphonate markers can identify even small calculi that are difficult to appreciate on a conventional KUB film (Figure 17–15). Differential radioactive uptake dependent on stone composition appreciated during in vitro studies cannot be appreciated on in vivo studies. Nuclear scintigraphy cannot delineate upper-tract anatomy in sufficient detail to help direct a therapeutic plan.

▶ Intervention

A. Conservative Observation

Most ureteral calculi pass and do not require intervention. Spontaneous passage depends on stone size, shape, location, and associated ureteral edema (which is likely to depend on the length of time that a stone has not progressed). Ureteral calculi 4–5 mm in size have a 40–50% chance of spontaneous passage. In contrast, calculi >6 mm have a >15% chance of spontaneous passage. This does not mean that a 1-cm stone will not pass or that a 1–2-mm stone will always pass uneventfully.

Medical expulsive therapy (MET) helps facilitate spontaneous passage of ureteral stones. An -α-blocker, nonsteroidal anti-inflammatory medications with or without low-dose steroids has been studied to optimize spontaneous ureteral stone passage; the efficacy of medical expulsive therapy is now being questioned. The vast majority of stones that pass do so within a 6-week period after the onset of symptoms. Ureteral calculi discovered in the distal ureter at the time of presentation have a 50% chance of spontaneous passage, in contrast to a 25% and 10% chance in the mid and proximal ureter, respectively.



▲ **Figure 17–15.** ***A:*** Scout abdominal radiograph demonstrating large left staghorn renal calculus. ***B:*** Nuclear scintigraphic evaluation of renal calculi. Posterior view demonstrating uptake on large left staghorn calculus after furosemide (Lasix) diuresis. Note right kidney with uptake in lower pole. ***C:*** Follow-up tomogram confirms calculus (*arrow*) in right lower pole missed on initial radiograph.

B. Dissolution Agents

The effectiveness of dissolution agents depends on stone surface area, stone type, volume of irrigant, and mode of delivery. Oral alkalinizing agents used for uric acid dissolution include sodium or potassium bicarbonate and potassium citrate. Extra care should be employed in patients susceptible to congestive heart failure or renal failure. Citrate is metabolized to bicarbonate and is available in a variety of preparations. Polycitra contains potassium and sodium citrate and citric acid. Bicitra contains only sodium citrate and citric acid. Food does not alter the effectiveness of these agents. Alternatively, orange juice alkalinizes urine. Intravenous alkalinization is effective with 1/6 molar sodium lactate.

Intrarenal alkalinization may be performed successfully under a low-pressure system (<25 cm water pressure).

This may be achieved through a percutaneous nephrostomy tube or an externalized retrograde catheter. Agents include sodium bicarbonate, 2–4 ampules in 1 L of normal saline, producing a urinary pH between 7.5 and 9.0. Tromethamine-E and tromethamine can produce urinary pHs of 8.0–10.5 and are especially effective with pH-sensitive calculi as in uric acid and cystine lithiasis.

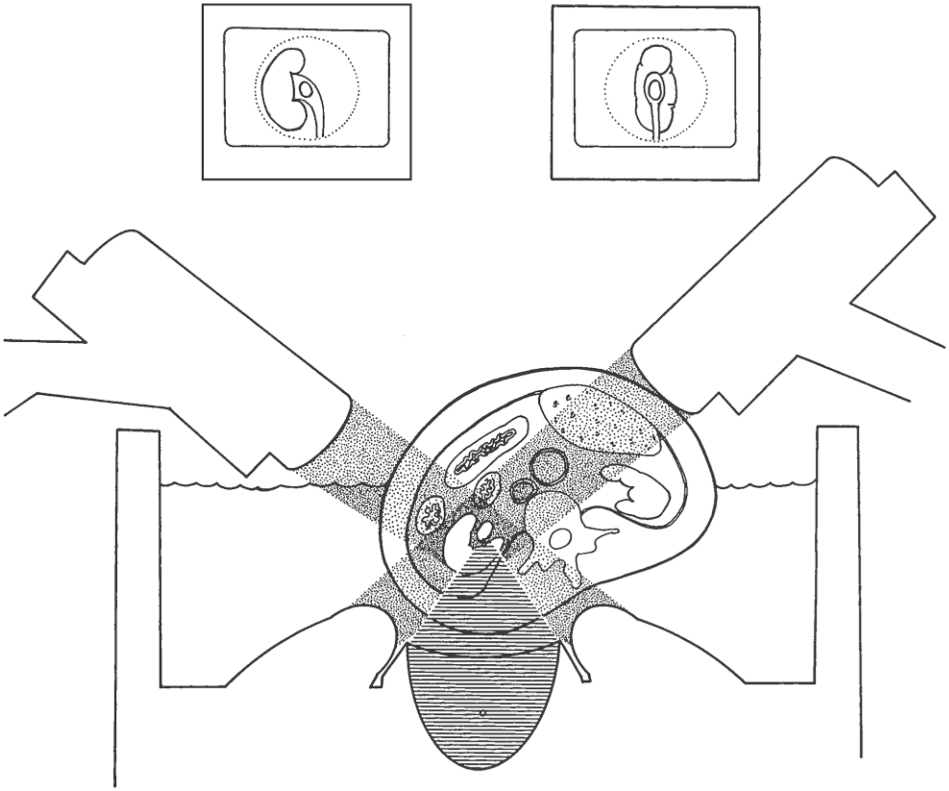
Struvite stone dissolution requires acidification and may be achieved successfully with Suby's G solution and hemiacidrin (Renacidin). Urinary pH may get down to 4.0. Hemiacidrin must be used with sterile urine, and careful monitoring of serum magnesium levels is required. The Food and Drug Administration (FDA) has not approved hemiacidrin for upper tract irrigations, and thus appropriate informed consent is required.

C. Relief from Obstruction

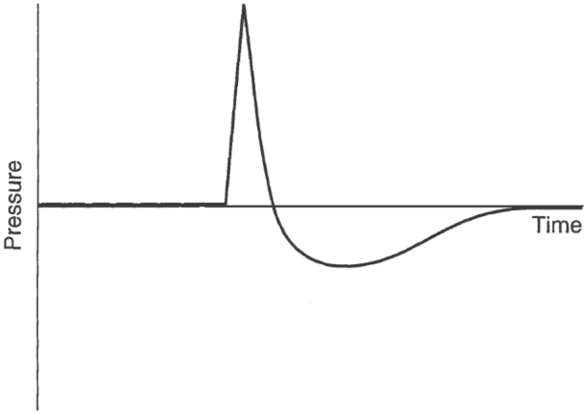
Urinary stone disease may result in significant morbidity and possible mortality in the presence of obstruction, especially with concurrent infection. A patient with obstructive urinary calculi with fever and infected urine requires emergent drainage. Retrograde pyelography to define upper tract anatomy is logically followed by retrograde placement of a double-J ureteral stent. On occasion, such catheters are unable to bypass the offending calculus or may perforate the ureter. In such situations, one must be prepared to place a percutaneous nephrostomy tube.

D. Extracorporeal Shockwave Lithotripsy

Extracorporeal SWL has revolutionized the treatment of urinary stones. The concept of using shock waves to fragment stones was noted in the 1950s in Russia. However, it was during the investigation of pitting on supersonic aircraft that Dornier, a German aircraft corporation, rediscovered that shockwaves originating from passing debris in the atmosphere can crack something that is hard. It was the ingenious application of a model developed in hopes of understanding such shockwaves that extracorporeal (outside the body) SWL emerged. The first clinical application with successful fragmentation of renal calculi was in 1980. The HM-1 (Human Model 1) lithotriptor underwent modifications in 1982 leading to the HM-2 and, finally, to the widespread application of the HM-3 in 1983 (Figure 17–16). Since then, thousands of lithotriptors have been put into use around the world, with millions of patients successfully treated.



▲ **Figure 17–16.** Diagrammatic representation of a Dornier HM-3 lithotriptor.



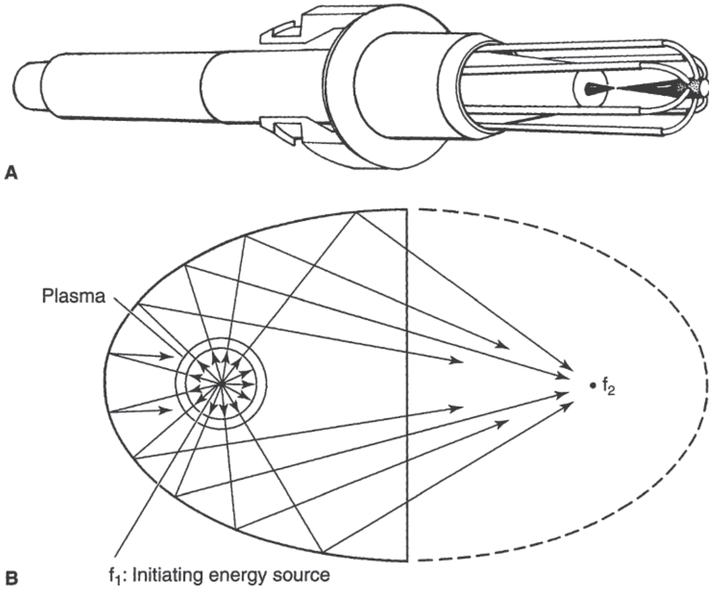
▲ **Figure 17–17.** Graphical representation of a shockwave. Vertical axis (ordinate) represents pressure and horizontal axis (abscissa) represents time.

All require an energy source to create the shockwave, a coupling mechanism to transfer the energy from outside to inside the body, and either fluoroscopic or ultrasonic modes, or both, to identify and position the calculi at a focus of converging shockwaves. They differ in generated pain and anesthetic or anesthesiologist requirements, consumable components, size, mobility, cost, and durability. Focal peak pressures (400–1500 bar), focal dimensions (6 × 28 mm to 50 × 15 mm), modular design, varied distances (12–17.0 cm) between focus 1 (the shockwave source) and focus 2 (the target), and purchase price differentiate the various machines.

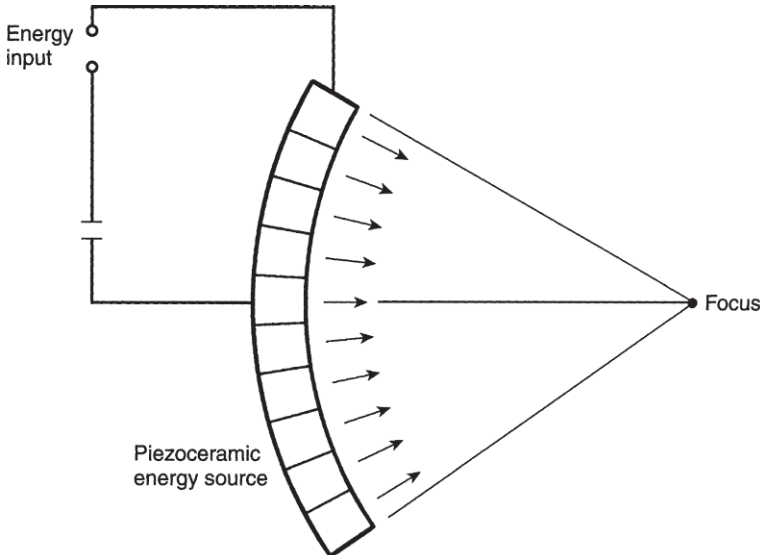
1. Shockwave physics—In contrast to the familiar ultrasonic wave with sinusoidal characteristics and longitudinal mechanical properties, acoustic shockwaves are not harmonic and have nonlinear pressure characteristics. There is a steep rise in pressure amplitude that results in compressive forces (Figure 17–17). There are two basic types of shockwave sources, supersonic and finite amplitude emitters.

Supersonic emitters release energy in a confined space, thereby producing an expanding plasma and an acoustic shockwave. Such shockwaves occur in nature—the familiar thunderstorm with lightning (an electrical discharge) followed by thunder (an acoustic sonic boom) is an analogous situation. Under controlled conditions, such an acoustic shockwave can successfully fragment calculi. The initial compression wave travels faster than the speed of sound in water and rapidly slows down to that speed. The traveling pressure wave is reduced in a nonlinear fashion. Medical applications have focused such waves to concentrate energy on a calculus (Figure 17–18).

Finite-amplitude emitters, in contrast to point-source energy systems, create pulsed acoustic shockwaves by displacing a surface activated by electrical discharge. There are two major types of finite-amplitude emitters: piezoceramic and electromagnetic. The piezoceramic variety results in a



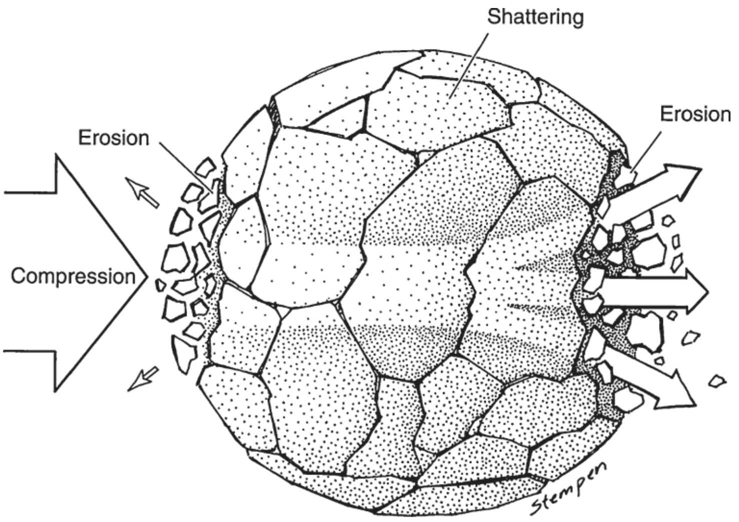
▲ **Figure 17–18.** ***A:*** Supersonic shockwave emission from a spark gap electrode. ***B:*** Reflecting the shockwave from focus 1 to focus 2 allows for stone fragmentation.



▲ **Figure 17–19.** Piezoceramic finite-amplitude emitter. Ceramic components are placed on the concave surface of a sphere, and each component is directed to an identified focus.

shockwave after an electrical discharge causes the ceramic component to elongate in such a manner that the surface is displaced and an acoustic pulse is generated. Thousands of such components placed on the concave side of a spherical surface directed toward a focus result in high stress, strain, and cavitation pressures (Figure 17–19). Electromagnetic systems are similar in concept to a stereo speaker system. An electrical discharge to a slab, adjacent to an insulating foil, creates an electric current that repulses a metal membrane, displacing it and generating an acoustic pulse into an adjacent medium. These waves need to be focused toward the offending stone.

All shockwaves, despite their source, are capable of fragmenting stones when focused. Fragmentation is achieved by erosion and shattering (Figure 17–20). Cavitational forces result in erosion at the entry and exit sites of the shockwave. Shattering results from energy absorption with stress, strain,



▲ **Figure 17–20.** Incoming shockwaves result in fragmentation from erosion and shattering.

and shear forces. Surrounding biologic tissues are resilient because they are neither brittle nor are the shockwaves focused on them.

Acoustic energy focusing (AEF) devices have been developed that can attach to the kidney stones. An external energy source with the appropriate resonant frequency will allow the AEF device to expand and then cavitate, resulting in stone fragmentation. Clinical trials are underway and may give an outpatient approach to fragmentating urinary stones.

2. Preoperative evaluation—Physical examination should be as thorough as in preparation for any other surgical procedure. Vital signs including blood pressure should be noted. Body habitus including any gross skeletal abnormalities, contractures, or excessive weight (>300 lb) may severely limit or preclude SWL. Borderline individuals require simulation before treatment. Pregnant women and patients with large abdominal aortic aneurysms or uncorrectable bleeding disorders should not be treated with SWL. Individuals with cardiac pacemakers should be thoroughly evaluated by a cardiologist. If SWL is contemplated, a cardiologist with thorough knowledge and with the ability to override the pacemaker should be present in the lithotripsy suite.

3. Intraoperative considerations

A. Stone localization—Proper patient positioning is a prerequisite for successful lithotripsy. Palpating the patient's ribs and pelvic bony girdle can approximate appropriate positioning. Anterior located kidneys, medial oriented portions of a horseshoe kidney, or transplant kidneys are best treated in the prone position. Understanding positioning options with the various lithotriptors is required to optimize therapy.

Small or poorly calcified calculi can be difficult to image with fluoroscopy, irrespective of their location. Placing a ureteral catheter identifies known anatomy and supplies an injection port for radiocontrast agents. A poorly calcified caliceal calculus can be identified by injecting dilute contrast agents into the collecting system and then focusing on the appropriate calyx or filling defect. In patients who cannot have retrograde stents placed, intravenous contrast agents may be used to help localize and thus focus on such stones.

B. Fluoroscopic imaging—The conditions for fluoroscopic imaging include appropriate collimation with dimmed room lighting to decrease radiation exposure and improve the quality of the fluoroscopic image. Intermittent fluoroscopy reveals movement of calculi with respiration and is helpful in locating and focusing on offending calculi.

C. Ultrasonic imaging—Ultrasound localization has the advantage of eliminating radiation exposure to the patient and the lithotripsy team. There are two basic types: the coaxial unit, aligned with the shockwave generator, and the articulating arm unit with a mobile transducer. Ultrasound easily can identify radiolucent or small calculi that are difficult to visualize with fluoroscopy. However, ureteral or other medially located calculi may be difficult or impossible to identify, especially in nonobstructive collecting systems. Visualization may be difficult or impossible with obese patients. Proficiency in ultrasound localization and assessment of fragmentation has a longer learning curve than that of fluoroscopy. Ultrasound images may be confusing when multiple stones or stone fragments are present.

D. Coupling—Successful fragmentation requires effective coupling. Coupling devices should have properties similar to those of human skin. Optimal systems should prevent pain, ecchymoses, hematomas, or skin breakdown. Interfaces between gas and tissue can result in tissue damage. Air bubbles entrapped by hair, by bandages from prior percutaneous procedures, or by inadequately degassed fluid or air in coupling cushions can significantly impede directed shockwaves and result in skin ecchymoses or breakdown. Despite adequate coupling, fragmentation may be inadequate owing to refraction and reflection of shockwaves at tissue interfaces, especially with obese patients.

The water bath provides the best coupling. Submersion of patients can result in profound hemodynamic changes, including peripheral venous compression, resulting in increased right atrial pressure, increased pulmonary capillary wedge pressure, and increased cardiac index. These hemodynamic changes should be appreciated, and appropriate monitoring should be used in individuals with marginal cardiovascular reserve. Such machines are infrequently available today.

In contrast, water cushion coupling systems have decreased water demands. A coupling gel like those used with ultrasonography provides an excellent interface with skin. The volume of such water cushions can frequently be adjusted to help focus calculi when patients are either extremely thin (eg, children) or obese. Very small patients may require an interposed bag (1–3 L) of normal saline to help with coupling. Both water coupling systems require degassed water to decrease water bubbles.

E. Shockwave triggering—Triggering shockwaves with the electrocardiogram was originally performed to decrease cardiac dysrhythmias. The lithotriptor would sense the large swing of the QRS complex and initiate the shockwave 20 ms (milliseconds) later; this would decrease shockwaves during the repolarization phase of the cardiac cycle (the myocardium is most sensitive during this time). Conceptually, it makes more sense to trigger the shockwaves in response to the respiratory cycle to optimize accurate focusing on the offending calculi that move with respiratory motion. Such systems are available. Most lithotriptors are now triggered without electrocardiogram gating and with unusual associated cardiac dysrhythmias. Slow rates of shockwaves have shown increased stone fragmentation efficiency.

F. Fragmentation—Safe shockwave dosage is unknown. Shockwaves induce trauma, including intrarenal and perirenal hemorrhage and edema, and thus the minimal shocks needed to achieve fragmentation should be delivered. Casual overtreatment should be avoided.

Determination of adequate fragmentation during treatment may be difficult. Initial sharp edges become fuzzy or blurred and have a shotgun-blast-like appearance. Stones that were initially visualized may disappear after successful fragmentation. Intermittent visualization ensures accurate focusing and assessment of progress and eventual termination of the procedure.

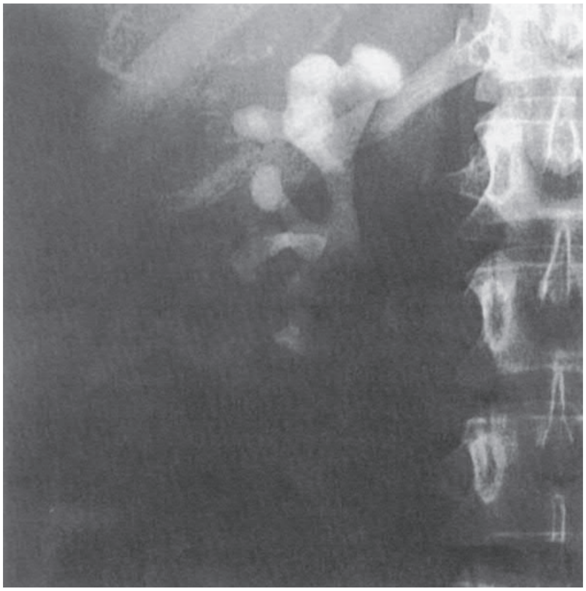
Bilateral nephrolithiasis may be treated in the same setting. One must first approach the side that is symptomatic or potentially more troublesome. If there is uncertainty concerning a large stone burden, one or more double-J catheters should be placed to decrease the likelihood of bilateral obstruction.

4. Postoperative care—Patients should be encouraged to maintain an active ambulatory status to facilitate stone passage. Gross hematuria should resolve during the first postoperative week. Fluid intake should be encouraged. Patients may return to work as soon as they feel comfortable in doing so.

Abdominal pain may be related to the shockwaves. Severe pain unresponsive to routine intravenous or oral medications should alert the physician for possible rare (0.66%) perirenal hematomas. In such a situation, CT scan should then be undertaken to stage the injury.

Shockwave lithotripsy is not associated with the development of hypertension. Stone burden correlates with postoperative complications. Steinstrasse (stone street) or accumulation and backup of stone gravel in a ureter can be frustrating. It should be specifically ruled out when postoperative radiographs are evaluated. Asymptomatic individuals can be followed up with serial KUBs and ultrasonography. Severe pain or fever requires intervention. Percutaneous nephrostomy drainage is usually uncomplicated owing to the associated hydronephrosis. Decompressing the collecting system allows for effective coaptation of the ureteral walls and encourages resolution of the problem. It is only in the rare patient that steinstrasse does not resolve with the procedures outlined; such cases require retrograde endoscopic manipulations to relieve the obstructed stone fragments. Usually, one finds one or two relatively large fragments that are obstructing. With their removal, the columniation of fragments resolves.

Patients with large renal pelvic calculi (1.5 cm) have a stone-free rate at 3 months approximating 75%, in comparison with those with a similar stone in a lower calyx, which approximates only 35%. Patients with small renal pelvic stones (<1.5 cm) have approximately a 90% stone-free rate in comparison with those with similar stones in a middle calyx (approximately 75%) or lower calyx (approximately 50%). Lower calyceal stone-free rates are increased with a small stone burden, a short and wide infundibulum, and a non-acute infundibulopelvic angle. Overall, approximately 75% of patients with renal calculi treated with SWL become stone-free in 3 months. As stones increase in size, stone-free rates decrease, more so in the lower and middle calyces than in superior calyceal and renal pelvic locations (Figure 17–21).



▲ **Figure 17–21.** Plain abdominal radiograph demonstrating complete staghorn calculus with the renal pelvic extending into all infundibula and calyces.

E. Ureteroscopic Stone Extraction

Ureteroscopic stone extraction is highly efficacious for lower ureteral calculi. The use of small-caliber ureteroscopes and the advent of balloon dilation or ureteral access sheaths have increased stone-free rates dramatically. Even relatively large-caliber endoscopes without balloon dilation are effective in lower ureteral stone retrieval. Reusable and disposable flexible ureteroscopes are routinely used and allow access to the entire upper collecting system. It is likely that disposable ureteroscopes will become more common to ensure a functional, clean, and available instrument. Stone-free rates approach 95–100% and are dependent on stone burden and location, length of time that the stone has been impacted, history of retroperitoneal surgery, and the experience of the operator. Complication rates are rare; the rates increase when manipulations venture into the proximal ureter. Calculi that measure <4–5 mm are frequently removed intact. Nitinol baskets are less traumatic than older round or flat-wired stone baskets. Excessive force with any instrument in the ureter may result in ureteral injury.

A variety of lithotrites can be placed through an ureteroscope, including electrohydraulic, solid and hollow-core ultrasonic probes, a variety of laser systems, and pneumatic systems such as the Swiss lithoclast. Electrohydraulic lithotrites have power settings as high as 120 V that result in a cavitation bubble, followed by collapse of this bubble, causing subsequent shockwaves. Care should be taken to keep the tip of the electrode away from surrounding tissue and the tip of the endoscope. Ultrasonic lithotrites have a piezoceramic energy source that converts electrical energy into ultrasonic waves in the range of 25,000 Hz. This vibratory action is effective in fragmenting calculi. Hollow probes can suction stone fragments and debris simultaneously. Laser systems (especially the holmium one) are discussed elsewhere in this book but are the most common lithotrite to fragment calculi. The electromechanical impactors are similar to jackhammers with a movable piston-like tip that fragments calculi.

F. Percutaneous Nephrolithotomy

Percutaneous removal of renal and proximal ureteral calculi is the treatment of choice for large (>2.0 cm) calculi; those resistant to SWL; select lower pole calyceal stones with a narrow, long infundibulum and an acute infundibulopelvic angle; and instances with evidence of obstruction; the method can rapidly establish a stone-free status. Needle puncture is directed by fluoroscopy, ultrasound, or both, and is routinely placed from the posterior axillary line into a posterior calyx. Superior caliceal puncture may be required, and in such situations, care should be taken to avoid injury to the pleura, lungs, spleen, and liver. Tract dilation is performed by sequential plastic dilators (Amplatz system), telescoping metal dilators (Alken), or balloon dilation. Tracts placed during open renal procedures are frequently tortuous and suboptimal for subsequent endourologic procedures.

Percutaneous extraction of calculi requires patience and perseverance. Residual calculi can be retrieved with the aid of flexible endoscopes, additional percutaneous puncture access, follow-up irrigations, SWL, or additional percutaneous sessions. Placing patients in a modified supine position allows for simultaneous percutaneous and ureteroscopic stone manipulations and limits the need for additional percutaneous punctures. Realistic goals should be established. Patients should be informed that complex calculi frequently require numerous procedures.

Maintenance of body temperature with appropriate blankets during preoperative patient positioning and the use of warmed irrigants during the actual procedure helps prevent bleeding diatheses associated with hypothermia. Blood transfusion rates are typically <4–5%. Multiple percutaneous punctures are associated with a greater blood loss. Overall, such procedures are safe and effective.

G. Open-Stone Surgery

Open-stone surgery is the historic way to remove calculi, yet it is rarely used today. The morbidity of the incision, the possibility of retained stone fragments, and the ease and success of less invasive techniques have made these procedures rare.

H. Other Renal Procedures

Partial nephrectomy is appropriate with a large stone burden in a renal pole with marked parenchymal thinning. Caution should be taken with a simple nephrectomy, even with a normal contralateral kidney, as stones are frequently associated with a systemic metabolic defect that may recur in the contralateral kidney. What may seem prudent and simple today may be regretted tomorrow.

Other unusual procedures include ileal ureter substitution performed with the hope of decreasing pain with frequent stone passage. Autotransplantation with pyelocystostomy is another option for patients with rare malignant stone disease.

I. Ureterolithotomy

Longstanding ureteral calculi—those inaccessible with endoscopy and those resistant to SWL—can be extracted with an ureterolithotomy. Again, a preoperative radiograph documents stone location and directs an appropriate incision. The proximal ureter may be approached with a dorsal lumbotomy. An incision lateral to the sacrospinalis muscles allows medial retraction of the quadratus lumborum. The anterior fascicle of the dorsal lumbar fascia must be incised to gain proper exposure despite the appearance of potentially opening the peritoneum. Once the ureter is identified, a vessel loop or a Babcock clamp should be placed proximal to the stone to prevent frustrating stone migration. Extension of this incision is limited superiorly by the 12th rib and inferiorly by the iliac crest. A longitudinal incision over the stone with a hooked blade exposes the calculus. The nerve hook is excellent to help tease out the stone. A flank or anterior abdominal muscle splitting incision gives excellent exposure to mid and distal ureteral stones.

▶ Prevention

In general, 50% of patients experience recurrent urinary stones within 5 years without prophylactic intervention. Appropriate education and preventive measures are best instituted with a motivated patient after spontaneous stone passage or surgical stone removal. Risk factors as described previously should be identified and modified, if possible. Irrespective of the final metabolic evaluation and stone analysis, the patient's fluid intake should result in about 1.5–2.0 L of urine/24 hours. Fluids should be encouraged during mealtime. In addition, liquids should be increased approximately 2 hours after meals. Water produced as a metabolic by-product reaches its nadir at this time, and thus the body is relatively dehydrated. Fluid ingestion also should be encouraged to force a nighttime diuresis adequate to awaken the patient to void. Awakening and ambulating to void limit urinary stasis and offer an opportunity to ingest additional fluids. These lifestyle changes are difficult to maintain and should be encouraged during subsequent office visits. Motivated patients who regularly return to a urinary stone clinic have a reduced stone recurrence rate that is probably due to increased compliance.

A. Metabolic Evaluation

A systematic metabolic evaluation should be instituted after a patient has recovered from urinary stone intervention or spontaneous stone passage. Stone analysis should be obtained to help direct the workup. An outpatient urine collection during typical activities and fluid intake helps unmask significant abnormalities. An initial 24-hour urine collection for calcium stone formers should include tests for calcium, uric acid, oxalate, citrate, phosphate, sulfate, sodium, volume, and pH. Twenty-four-hour urine values help direct appropriate prophylactic therapy. An open dialog with local laboratories helps standardize collection routines and determine whether an outside laboratory is preferred. Baseline serum levels for blood urea nitrogen, creatinine, calcium (with or without parathyroid hormone), phosphorous, and uric acid are appropriate.

B. Oral Medications

1. Alkalinizing pH agents—Potassium citrate is an oral agent that elevates urinary pH effectively by 0.7–0.8 pH units. Typical dosing is 60 mEq in three or four divided doses daily. It is available in wax matrix 10- or 15-mEq tablets, liquid preparations, and crystals that must be mixed with fluids. The effect is maintained over many years. Care should be taken in patients susceptible to hyperkalemia, those with renal failure, and those taking potassium-sparing diuretics. Although the medication is usually well tolerated, some patients may complain of abdominal discomfort, especially with tablet preparations. It is indicated in those with calcium oxalate calculi secondary to hypocitraturia (<450 mg/day), including those with renal tubular acidosis. Potassium citrate also may be used effectively to treat uric acid lithiasis and milder forms of hyperuricosuric calcium nephrolithiasis. There are no effective long-term urinary acidifying agents.

2. Gastrointestinal absorption inhibitor—Cellulose phosphate binds calcium in the gut and thereby inhibits calcium absorption and urinary excretion and is appropriate for patients with type 1 absorptive hypercalciuria. Patients should have normal parathyroid hormone and serum calcium and phosphate values, no evidence of bone disease, and evidence of increased intestinal calcium absorption. The drug decreases the urinary saturation of calcium phosphate and calcium oxalate. It may increase urinary oxalate and urinary phosphate levels. A typical starting dosage is 5 g thrice (3 times) daily with meals; the dosage may be titrated by following 24-hour urinary calcium levels. Urinary magnesium, calcium, oxalate, and sodium levels and serum parathyroid hormone should be monitored 1 or 2 times yearly. Magnesium supplements are frequently required and should be taken at least 1 hour before or after cellulose phosphate is ingested. Cellulose phosphate is associated with a sodium load and should be used with caution in those with congestive heart failure. Gastrointestinal side effects are infrequent; they include dyspepsia and loose bowel movements.

Cellulose phosphate may be suboptimal treatment for postmenopausal women who are at risk for bone disease. An alternative treatment for such patients would be hydrochlorothiazides supplemented with potassium citrate to offset the potential hypokalemia and hypocitraturia.

3. Phosphate supplementation—Renal phosphate leak is best treated by replacing phosphate. Phosphate absorption may be inhibited in the presence of aluminum-, magnesium-, or calcium-containing antacids. This treatment should be used with caution in digitalized patients and in those with severe renal failure, Addison's disease, or severe hepatic dysfunction. It is generally well tolerated. Dosing can begin with 250 mg 3 or 4 times daily and may be doubled depending on follow-up serum electrolyte, calcium, and phosphorus levels.

4. Diuretics—Thiazides can correct the renal calcium leak associated with renal hypercalciuria. This prevents a secondary hyperparathyroid state and its associated elevated vitamin D synthesis and intestinal calcium absorption. A rapid decrease in urinary calcium excretion is appreciated and is sustained long term (>10 years). A starting dose of 25 mg may be titrated on the basis of urinary calcium levels. Side effects are usually well tolerated. Potassium levels should be monitored. Hypokalemia induces a hypocitraturic state; potassium replacement corrects the hypokalemia and its associated hypocitraturia.

Thiazides result in a transient decrease in urinary calcium excretion in absorptive hypercalciurics. Urinary calcium excretion rebounds to pretreatment values in 50% of such patients after 4–5 years of therapy. Dietary changes are not believed to be responsible for this phenomenon. Thiazides do not restore normal intestinal absorption of calcium.

5. Calcium supplementation—Enteric hyperoxaluric calcium nephrolithiasis is effectively treated with calcium supplements. Calcium gluconate and calcium citrate are better absorbed and are more effective in increasing serum calcium availability than are other forms of calcium. Calcium carbonate, calcium phosphate, and oyster shells are forms of calcium that are less efficiently absorbed; they remain in the intestinal lumen, available to bind oxalate, thus reducing its absorption. These less efficiently absorbed forms of calcium are optimal to treat enteric hyperoxaluric calcium nephrolithiasis and must be given with meals to be effective.

6. Uric acid–lowering medications—Allopurinol is used to treat hyperuricosuric calcium nephrolithiasis with or without hyperuricemia. Unlike uricosuric agents that reduce serum uric acid levels by increasing urinary uric acid excretion, allopurinol is a xanthine–oxidase inhibitor and reduces both serum and urinary levels of uric acid. It has no impact on the biosynthesis of purines; rather, it acts exclusively on purine catabolism. Elevated levels of xanthine and hypoxanthine in the urine secondary to allopurinol have not been associated with nephrolithiasis. Allopurinol is a potentially dangerous drug and should be discontinued at the first appearance of a skin rash, which infrequently may be fatal. Therapy can start at 300 mg/day. It is tolerated best when taken after meals.

7. Urease inhibitor—Acetohydroxamic acid is an effective adjunctive treatment in those with chronic urea-splitting urinary tract infections associated with struvite stones. Acetohydroxamic acid reversibly inhibits bacterial urease, decreasing urinary ammonia levels, and will subsequently acidify urine. It is best used as prophylaxis after removal of struvite stones. It also may be used after unsuccessful attempts at curative surgical removal of calculi or culture-specific antibiotic therapy. Patients with serum creatinine >2.5 mg/dL are unable to achieve therapeutic urinary levels. Acetohydroxamic acid is not effective with non-urease-producing bacteria. Long-term data (>7 years) are unavailable. A significant number of patients complain of side effects, including headaches that are usually short-lived and responsive to aspirin compounds. Other frequent complaints include nausea, vomiting, anorexia, nervousness, and depression. A typical dosing regimen is one 250-mg tablet 3 or 4 times daily (total daily dosage: 10–15 mg/kg).

8. Prevention of cystine calculi—Conservative measures, including massive fluid intake and urinary alkalinization, are frequently inadequate to control cystine stone formation. Penicillamine, the same drug that is used to chelate excess copper in the treatment of Wilson's disease, undergoes a thiol–disulfide exchange with cystine. This reduces the amount of urinary cystine that is relatively insoluble. Cystine solubility is pH dependent (pH 5.0: 150–300 mg/L; pH 7.0: 200–400 mg/L; pH 7.5: 220–500 mg/L). ᴅ-Penicillamine is associated with numerous and frequent side effects, including rashes and hematologic, renal, and hepatic abnormalities. An initial dosage of 250 mg daily in three to four divided doses may help reduce severe side effects. It may be increased gradually to 2 g/day. Dosage should be titrated with quantitative urinary cystine values. Penicillamine increases the requirement of pyridoxine (vitamin B_6), which should be supplemented with 25–50 mg/day.

Mercaptopropionylglycine (Thiola) is better tolerated by patients than is penicillamine. Mercaptopropionylglycine, a reducing agent, binds to the sulfide portion of cystine, forming a mixed disulfide (Thiola-cysteine) water-soluble compound. It may retard the rate of new stone formation. The dosage should be titrated with repeat 24-hour urinary cystine values. An initial dosage may be 200–300 mg 3 times daily, either 1 hour before or 2 hours after each meal. Side effects are not infrequent and may include drug fever; nausea, vomiting, and gastrointestinal upset; rash, wrinkling, or friable skin; lupus-like symptoms, decreased taste perception; and a variety of hematologic disorders.

BLADDER STONES

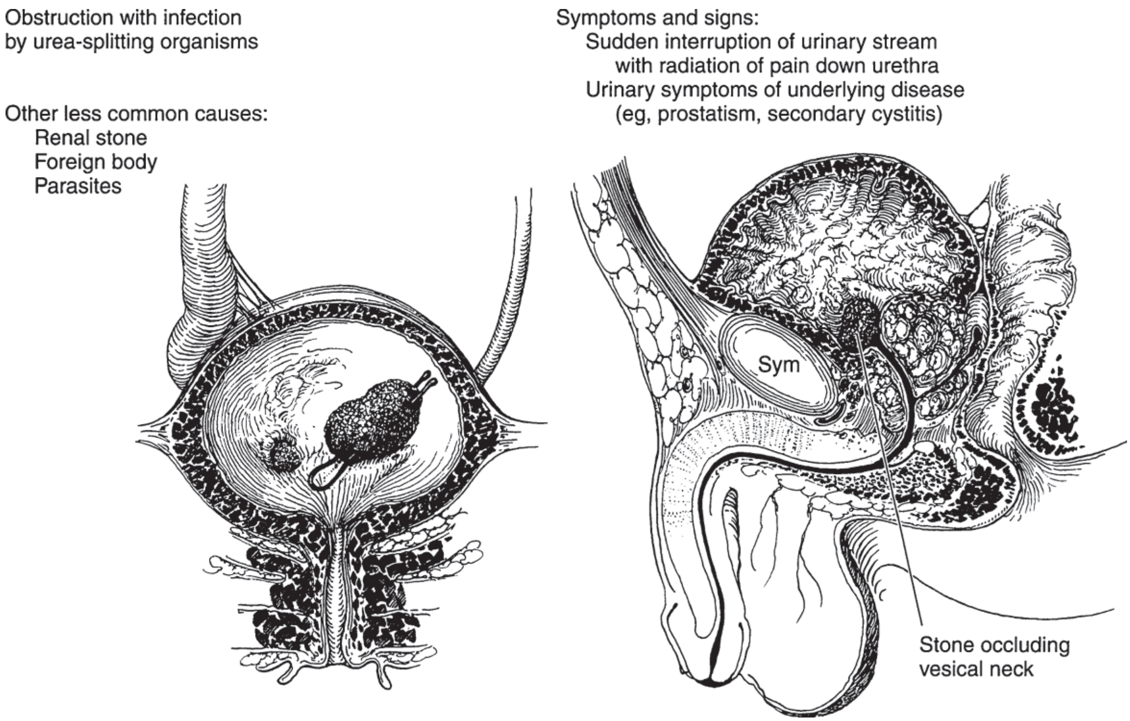
Bladder calculi usually are a manifestation of an underlying pathologic condition, including voiding dysfunction or a foreign body. Voiding dysfunction may be due to a urethral stricture, benign prostatic hyperplasia, bladder neck contracture, or flaccid or spastic neurogenic bladder, all of which result in static urine. Foreign bodies such as Foley catheters and forgotten double-J ureteral catheters can serve as nidi for stones (Figure 17–22). Most bladder calculi are seen in men. In developing countries, they are frequently found in prepubescent boys. Stone analysis frequently reveals ammonium urate, uric acid, or calcium oxalate stones. Bladder stones can be solitary or numerous (Figure 17–23). Patients present with irritative voiding symptoms, intermittent urinary stream, urinary tract infections, hematuria, or pelvic pain. Physical examination is unrevealing. A large percentage of bladder stones are radiolucent (uric acid). Ultrasound of the bladder identifies the stone with its characteristic postacoustic shadowing. The stone moves with changing body position.

Stones within a ureterocele do not move with body position (Figure 17–24) as seen on ultrasound examination. They frequently are nonobstructive. Endoscopic incision and stone removal rarely results in vesicoureteral reflux. The mode of stone removal for other bladder stones should be directed by the underlying cause.

Early instruments used to remove bladder calculi were both clever and bizarre. Simple mechanical crushing devices are still used today. Mechanical lithotrites should be used with caution to prevent bladder injury when the jaws are closed. Ensuring a partially full bladder and endoscopic visualization of unrestricted lateral movement before forceful crushing of the stones helps reduce this troublesome complication. Cystolitholapaxy allows most stones to be broken and subsequently removed through a cystoscope. Electrohydraulic, ultrasonic, laser, and pneumatic lithotrites similar to those used through a nephroscope are effective. Cystolithotomy can be performed through a small abdominal incision.

PROSTATIC AND SEMINAL VESICLE STONES

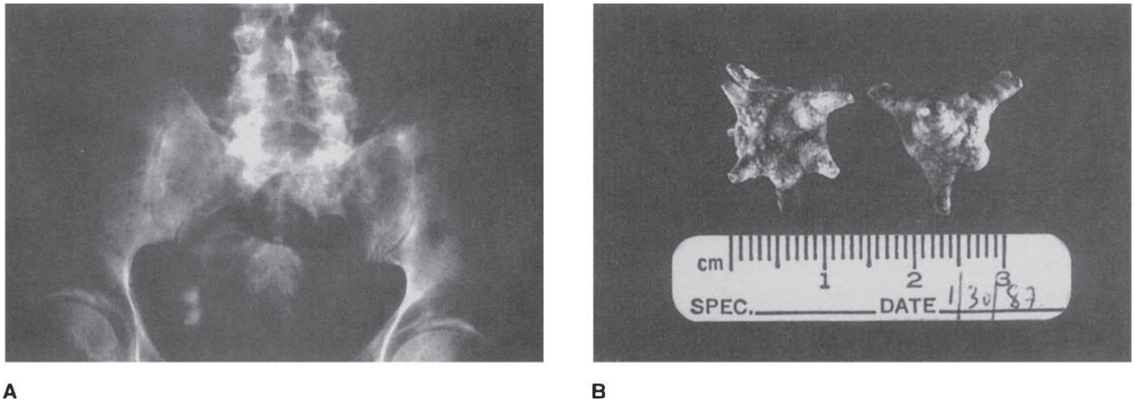
Prostatic calculi are found within the prostate gland per se and are found uncommonly within the prostatic urethra. They are thought to represent calcified corpora amylacea and are rarely found in boys. Usually small and numerous, they are noted to be tannish gray in color during transurethral resection of the prostate. They are commonly located at the margin of the


Obstruction with infection
by urea-splitting organisms
Other less common causes:
Renal stone
Foreign body
Parasites
Symptoms and signs:
Sudden interruption of urinary stream
with radiation of pain down urethra
Urinary symptoms of underlying disease
(eg, prostatism, secondary cystitis)
Sym
Stone occluding
vesical neck

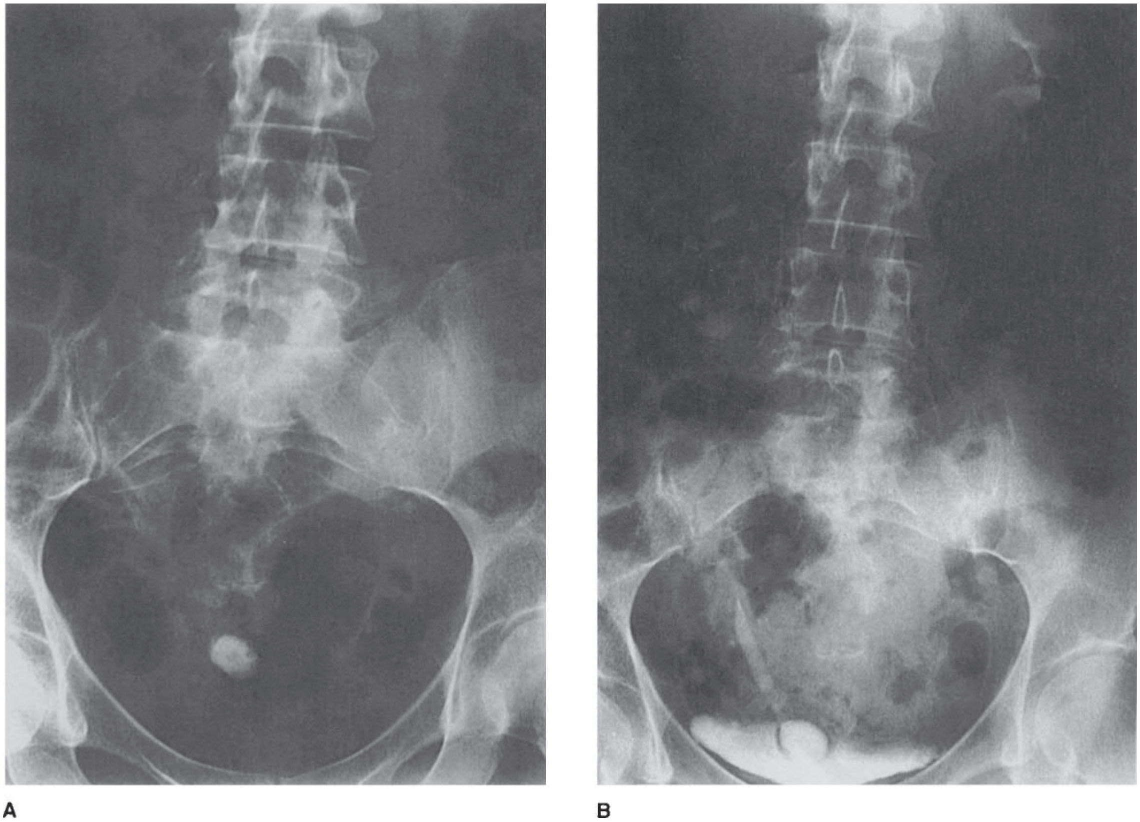
▲ **Figure 17–22.** Genesis and symptoms and signs of vesical calculus.

surgically resected adenoma and are composed of calcium phosphate. Although usually of no clinical significance, they are occasionally associated with chronic prostatitis. Large prostatic calculi may be misinterpreted as a carcinoma. The prostate is usually mobile, however, and a radiograph or transrectal ultrasound helps to confirm the diagnosis.

Seminal vesicle stones are smooth and hard and are extremely rare. They may be associated with hematospermia. Physical examination reveals a stony hard gland, and when multiple stones are present, a crunching sensation may be noted. These stones occasionally are confused with tuberculosis of the seminal vesicle.



▲ **Figure 17–23.** ***A:*** Plain abdominal radiograph demonstrating two bladder calculi. ***B:*** Gross picture of removed bladder calculi. Note the characteristic shape of jackstones typically composed of uric acid.



▲ **Figure 17–24.** ***A:*** Scout abdominal radiograph demonstrating extraosseous calcification in the region of the bladder. ***B:*** Intravenous pyelogram demonstrates a stone to be within a ureterocele.

URETHRAL AND PREPUTIAL STONES

Urethral calculi usually originate from the bladder and rarely from the upper tracts. Most ureteral stones that pass spontaneously into the bladder can pass through the urethra unimpeded. Urethral stones may develop secondary to urinary stasis, secondary to a urethral diverticulum, near urethral strictures, or at sites of previous surgery. Most urethral stones in men present in the prostatic or bulbar regions and are solitary. Patients with recurrent pendulous urethral calculi without evidence of other pathologic conditions should be suspected of self-introduction of such stones while attempting to obtain pain medications or for attention, as seen in Munchausen syndrome.

Females rarely develop urethral calculi because of their short urethra and a lower incidence of bladder calculi. Most urethral stones found in women are associated with urethral diverticula.

Symptoms are similar to those of bladder calculi—intermittent urinary stream, terminal hematuria, and infection. The stones may present with dribbling or during acute urinary retention. Pain may be severe and, in men, may radiate to the tip of the penis. The diagnosis may be confirmed by palpation, endoscopic visualization, or radiographic study.

Treatment should be directed by the underlying cause. Stones associated with a dense urethral stricture or complex diverticula can be removed during definitive open surgical repair. Small stones may be grasped successfully and removed intact. More frequently, they need to be fragmented and removed. Longstanding, large impacted stones are best removed through a urethrotomy.

Preputial calculi are rare and usually occur in adults. They develop secondarily to a severe obstructive phimosis. They may occur secondarily to poor hygiene with inspissated smegma. Diagnosis is confirmed by palpation. Treating the underlying cause with a dorsal preputial slit or a formal circumcision prevents recurrent calculi.

BIBLIOGRAPHY

Urinary Ions

Calcium

Milosevic D et al: Determination of urine saturation with computer program EQUIL 2 as a method for estimation of the risk of urolithiasis. J Chem Inf Comput Sci 1998;38:646.

Moe OW, Bonny O: Genetic hypercalciuria. J Am Soc Nephrol 2005;16:729.

Traxer O et al: Effect of ascorbic acid consumption on urinary stone risk factors. J Urol 2003;170(2, Pt 1):397–401.

Wallace RB et al: Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. Am J Clin Nutr 2011;94(1):270–277.

Oxalate

Knight J et al: Metabolism of fructose to oxalate and glycolate. Horm Metab Res 2010;42(12):868–873.

Thurgood LA et al: Comparison of the specific incorporation of intracrystalline proteins into urinary calcium oxalate monohydrate and dihydrate crystals. J Proteome Res 2010;9(9):4745–4757.

Tiselius HG: Standardized estimate of the ion activity product of calcium oxalate in urine from renal stone formers. Eur Urol 1989;16:48.

Uric Acid

Maalouf NM: Metabolic syndrome and the genesis of uric acid stones. J Ren Nutr 2011;21(1):128–131.

Marangella M: Uric acid elimination in the urine. Pathophysiological implications. Contrib Nephrol 2005;147:132.

Stoller ML: Gout and stones or stones and gout? J Urol 1995;154:1670.

Cystine

Purohit RS, Stoller ML: Stone clustering of patients with cystine urinary stone formation. Urology 2004;63:630.

Shekarriz B, Stoller ML: Cystinuria and other noncalcareous calculi. Endocrinol Metab Clin North Am 2002;31:951.

Zee T et al: Alpha lipoic acid treatment prevents cystine urolithiasis in a mouse model of cystinuria. Nat Med 2017;23(3):288.

Xanthine

Gargah T et al: Xanthine urolithiasis. Saudi J Kidney Dis Transpl 2010;21(2):328–331.

Triamterene

Daudon M, Jungers P: Drug-induced renal calculi: Epidemiology, prevention and management. Drugs 2004;64(3):245–275.

Urinary Stone Inhibitors

Citrate

Seltzer MA et al: Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. J Urol 1996;156:907.

Shah O et al: Genetic and dietary factors in urinary citrate excretion. J Endourol 2005;19:177.

Spivacow FR et al: Long-term treatment of renal lithiasis with potassium citrate. Urology 2010;76(6):1346–1349.

Urinary Proteins

Selvam R, Kalaiselvi P: Oxalate binding proteins in calcium oxalate nephrolithiasis. Urol Res 2003;31:242.

Trace Elements

Schwartz BF et al: Rethinking the role of urinary magnesium in calcium urolithiasis. J Endourol 2001;15:233.

Etiology

Hsi RS et al: The origins of urinary stone disease: Upstream mineral formation initiate downstream Randall's plaque. BJU Int; 2017;119(1):177.

Renal Tubular Acidosis

Evan AP et al: Renal histopathology of stone-forming patients with distal renal tubular acidosis. Kidney Int 2007;71(8):795–801.

Metabolic Workup

Meschi T et al: Body weight, diet and water intake in preventing stone disease. Urol Int 2004;72(Suppl 1):29–33.

Tiselius HG et al: Metabolic work-up of patients with urolithiasis: indications and diagnostic algorithm. Eur Urol Focus; 2017;3(1):62.

Urinary Stone Disease in Uncommon Situations

Spinal Cord Dysfunction

Ramsey S, McIlhenny C: Evidence-based management of upper tract urolithiasis in the spinal cord-injured patient. Spinal Cord 2011;49(9):948–954.

Pregnancy

Reinstatler L et al: Association of pregnancy with stone formation among women in the United States: A NHANES analysis 2007 to 2012. J Urol 2017.

Renal Transplantation

Lu HF et al: Donor-gifted allograft urolithiasis: Early percutaneous management. Urology 2002;59:25.

Obesity

Nowfar S et al: The relationship of obesity and gender prevalence changes in United States inpatient nephrolithiasis. Urology 2011;78(5):1029–1033.

Taylor EN et al: Obesity, weight gain, and the risk of kidney stones. JAMA 2005;293:455.

Anatomic Renal Anomalies

Baskin LS et al: The horseshoe kidney: Therapeutic considerations with urolithiasis. J Endourol 1989;3:51.

Chaudry R et al: Percutaneous stone surgery in spina bifid patients – are stone free rates worth the risk? J Endourol 2017;(S1):81.

Ganpule AP, Desai MR: Urolithiasis in kidneys with abnormal lie, rotation or form. Curr Opin Urol 2011;21(2):145–153.

Pediatrics

Tasian GE et al: Kidney stone recurrence among children and adolescents. J Urol 2017;197(1):246.

Caliceal Diverticulae

Gross AJ, Herrmann TR: Management of stones in calyceal diverticulum. Curr Opin Urol 2007;17(2):136–140.

Tumors

Paonessa J et al: Squamous cell carcinoma of the renal pelvis associated with kidney stones: A case report. Med Oncol 2010;28(Suppl 1): S392–S394.

Medical Therapy

Berger AD et al: Patients with primary hyperparathyroidism—why do some form stones? J Urol 2009;181(5):2141–2145.

Kenny JE, Goldfarb DS: Update on the pathophysiology and management of uric acid renal stones. Curr Rheumatol Rep 2010; 12(2): 125–129.

Pak CY et al: Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. J Urol 2001;165:378–381.

Song L et al: 24-hour urine calcium in the evaluation and management of nephrolithiasis. JAMA 2017;318(5):474.

Surgical Therapy

Al-Kohlany KM et al: Treatment of complete staghorn stones: A prospective randomized comparison of open surgery versus percutaneous nephrolithotomy. J Urol 2005;173:469.

Turk C et al: EAU guidelines on interventional treatment of urolithiasis. Eur Urol 2016;69(3):475.

Extracorporeal Shockwave Lithotripsy

Chaussy CG et al: First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. J Urol 1982;127:417.

Drach GW et al: Report of the United States co-operative study of extracorporeal shock wave lithotripsy. J Urol 1986;135:1127.

Elbahnasy AM et al: Lower caliceal stone clearance after shock wave lithotripsy or ureteroscopy: The impact of lower pole radiographic anatomy. J Urol 1998;159:676.

Lingeman JE et al: Blood pressure changes following extracorporeal shock wave lithotripsy and other forms of treatment for nephrolithiasis. JAMA 1990;263:1789.

Percutaneous Nephrostolithotomy

Akman T et al: Factors affecting bleeding during percutaneous nephrolithotomy: Single surgeon experience. J Endourol 2011; 25(2):327–333.

Breda A et al: The evaluation of radiologic methods for access guidance in percutaneous nephrolithotomy: A systematic review of the literature. Scand J Urol 2017.

Irby PB et al: Percutaneous access techniques in renal surgery. Tech Urol 1999;5:29.

Ureteroscopy

Bagley DH: Removal of upper urinary tract calculi with flexible ureteropyeloscopy. Urology 1990;35:412.

Doizi S, Traxer O: Flexible ureteroscopy: Technique, tips and tricks. Urolithiasis 2018;46(1):47–58.

This page intentionally left blank

Injuries to the Genitourinary Tract

18

Benjamin N. Breyer, MD, MAS, FACS

EMERGENCY DIAGNOSIS AND MANAGEMENT

About 10% of all injuries seen in the emergency room involve the genitourinary system to some extent. Many of them are subtle and difficult to define and require great diagnostic expertise. Early diagnosis is essential to prevent serious complications.

Initial assessment should include control of hemorrhage and shock along with resuscitation as required. Resuscitation may require intravenous lines and a urethral catheter in seriously injured patients. In men, before the catheter is inserted, the urethral meatus should be examined carefully for the presence of blood.

The history should include a detailed description of the accident. In cases involving gunshot wounds, the type and caliber of the weapon should be determined, since high-velocity projectiles cause much more extensive damage.

The abdomen and genitalia should be examined for evidence of contusions or subcutaneous hematomas, which might indicate deeper injuries to the retroperitoneum and pelvic structures. Fractures of the lower ribs are often associated with renal injuries, and pelvic fractures often accompany bladder and urethral injuries. Diffuse abdominal tenderness is consistent with perforated bowel, free intraperitoneal blood or urine, or retroperitoneal hematoma. Patients who do not have life-threatening injuries and whose blood pressure is stable can undergo more deliberate radiographic studies. This provides more definitive staging of the injury.

INJURIES TO THE KIDNEY (FIGURES 18–1 THROUGH 18–3)

Renal injuries are the most common injuries of the urinary system. The kidney is well protected by heavy lumbar muscles, vertebral bodies, ribs, and the viscera anteriorly. Fractured ribs and transverse vertebral processes may penetrate the renal parenchyma or vasculature. Most injuries occur from automobile accidents or sporting mishaps, chiefly in men and boys. Kidneys with existing pathologic conditions such as hydronephrosis or malignant tumors are more readily ruptured from mild trauma.

Etiology (Figure 18–4)

Blunt trauma directly to the abdomen, flank, or back is the most common mechanism, accounting for 80–85% of all renal injuries. Trauma may result from motor vehicle accidents, fights, falls, and contact sports. Vehicle collisions at high speed may result in major renal trauma from rapid deceleration and cause major vascular injury. Gunshot and knife wounds cause most penetrating injuries to the kidney; any such wound in the flank area should be regarded as a cause of renal injury until proven otherwise. Associated abdominal visceral injuries are present in 80% of renal penetrating wounds.

Pathology and Classification (Figure 18–5)

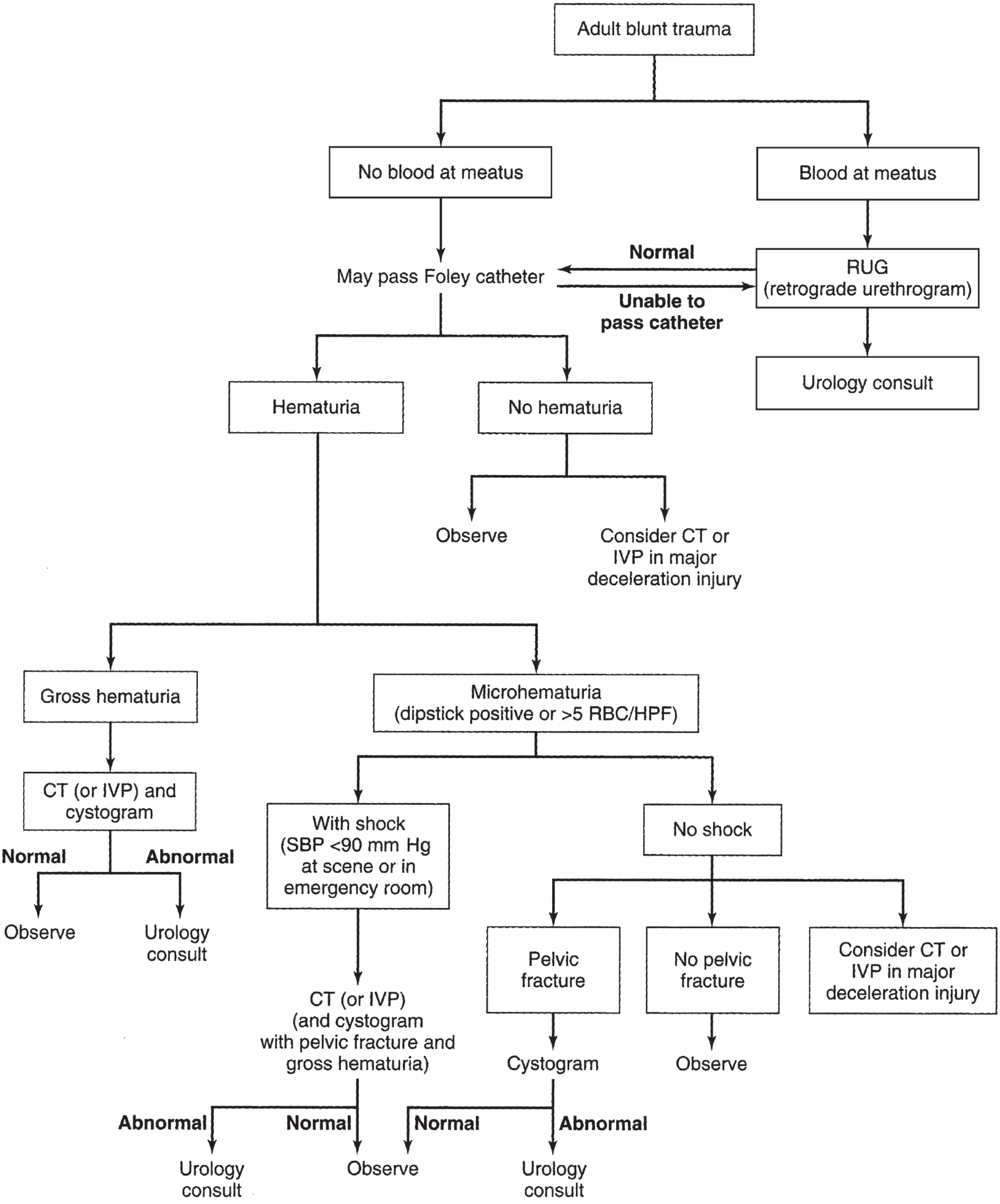
A. Early Pathologic Findings

Lacerations from blunt trauma usually occur in the transverse plane of the kidney. The mechanism of injury is assumed to be force transmitted from the center of the impact to the renal parenchyma. In injuries from rapid deceleration, the kidney moves upward or downward, causing sudden stretch on the renal pedicle and sometimes complete or partial avulsion. Acute thrombosis of the renal artery may be caused by an intimal tear from rapid deceleration injuries owing to the sudden stretch.

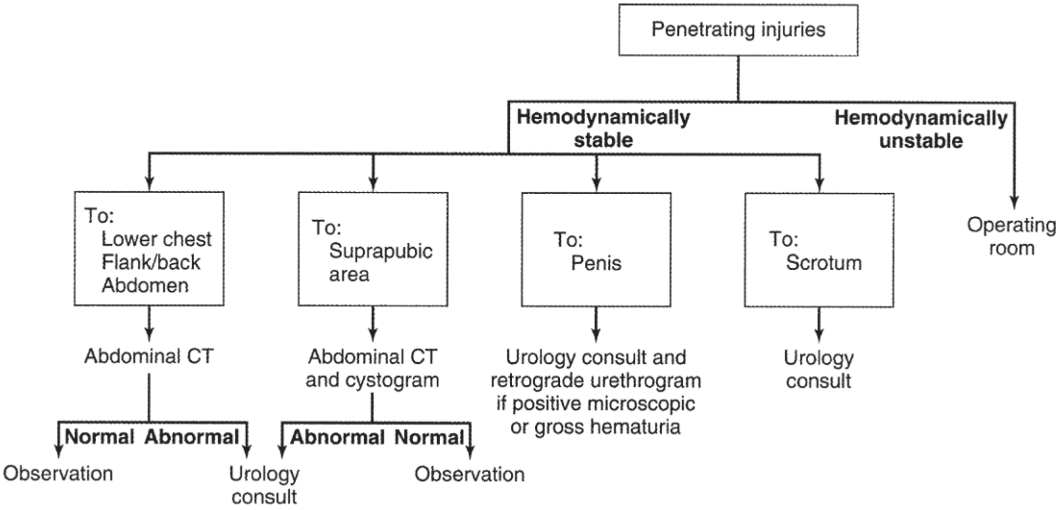
Pathologic classification of renal injuries is as follows:

Grade I (the most common)—Renal contusion or bruising of the renal parenchyma. Microscopic hematuria is common, but gross hematuria rarely occurs.

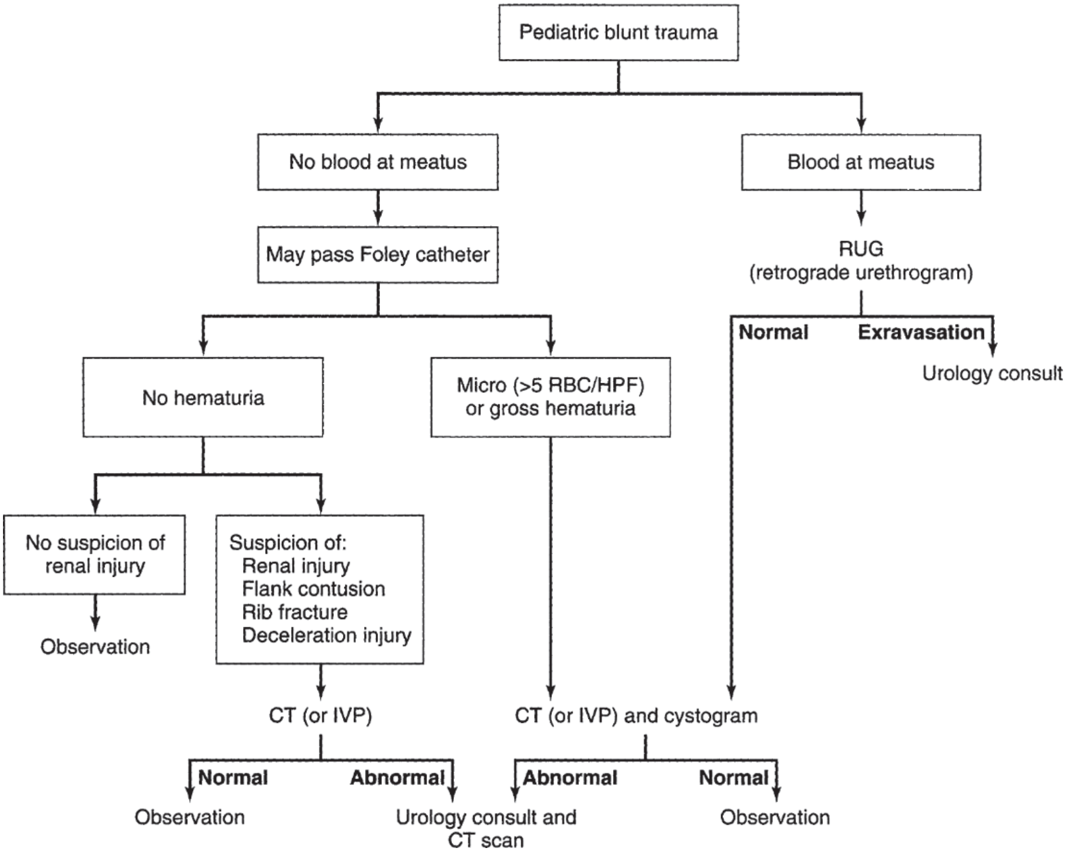
Grade II—Renal parenchymal laceration into the renal cortex (<1 cm). Perirenal hematoma is usually small.


Adult blunt trauma
No blood at meatus
Blood at meatus
May pass Foley catheter
Normal
Unable to pass catheter
RUG (retrograde urethrogram)
Urology consult
Hematuria
No hematuria
Observe
Consider CT or IVP in major deceleration injury
Gross hematuria
Microhematuria (dipstick positive or >5 RBC/HPF)
CT (or IVP) and cystogram
Normal
Abnormal
Observe
Urology consult
With shock (SBP <90 mm Hg at scene or in emergency room)
No shock
Pelvic fracture
No pelvic fracture
Consider CT or IVP in major deceleration injury
CT (or IVP) (and cystogram with pelvic fracture and gross hematuria)
Cystogram
Observe
Abnormal
Normal
Normal
Abnormal
Urology consult
Observe
Urology consult

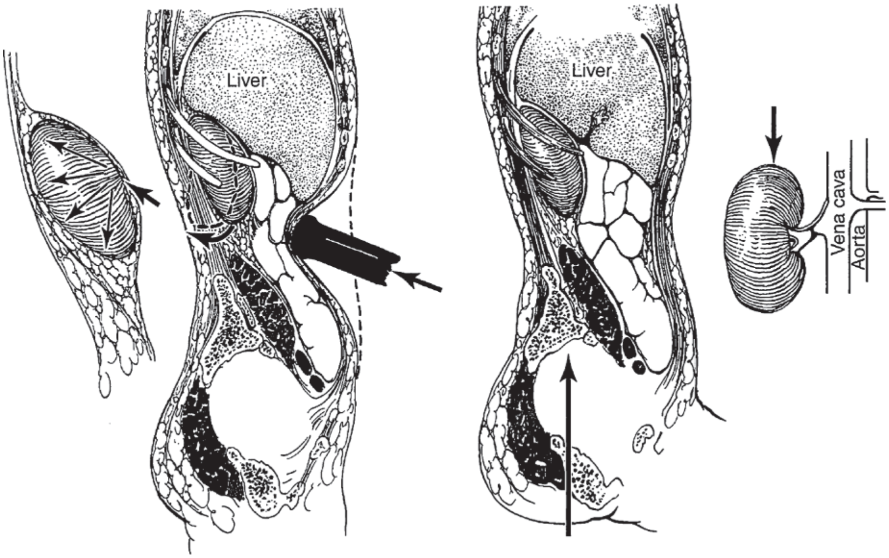
▲ **Figure 18–1.** Algorithm for staging blunt trauma in adults.



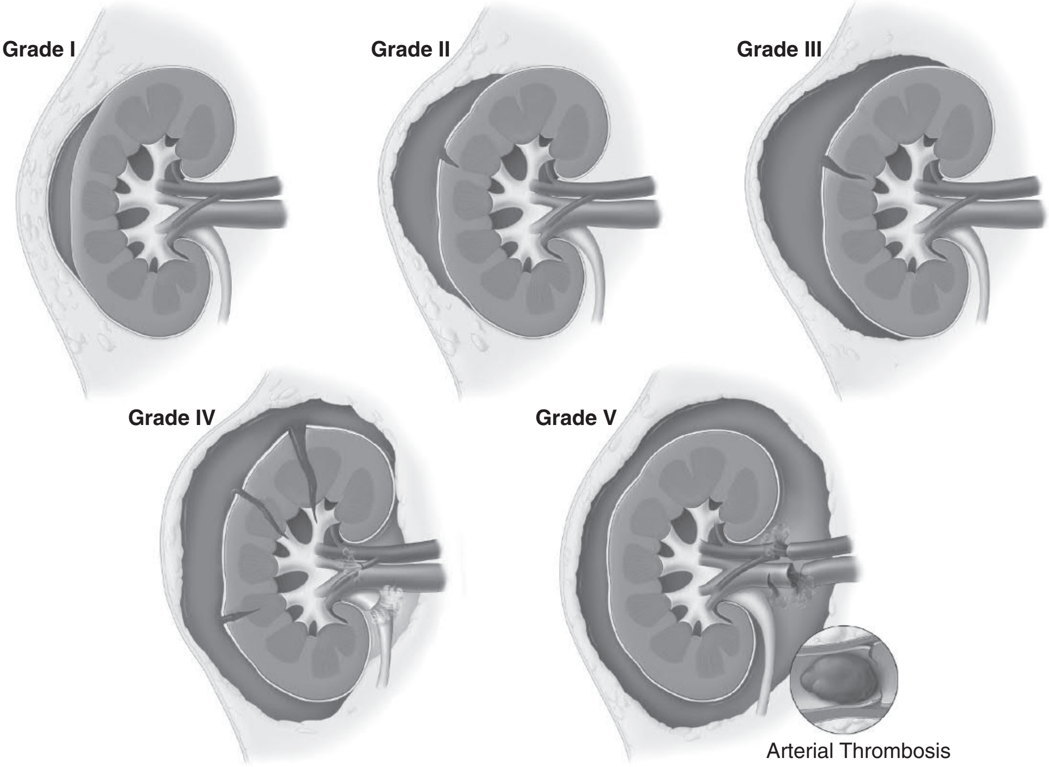
▲ **Figure 18–2.** Algorithm for staging penetrating trauma in adults.



▲ **Figure 18–3.** Algorithm for staging blunt trauma in children.



▲ **Figure 18–4.** Mechanisms of renal injury. ***Left:*** Direct blow to abdomen. Smaller drawing shows force of blow radiating from the renal hilum. ***Right:*** Falling on buttocks from a height (contrecoup of kidney). Smaller drawing shows direction of force exerted on the kidney from above. Tear of renal pedicle.



▲ **Figure 18–5.** Pathology-based classification of renal injuries.

Grade III—Renal parenchymal laceration extending through the cortex and into the renal medulla (>1 cm). Bleeding can be significant in the presence of large retroperitoneal hematoma.

Grade IV—Renal parenchymal laceration (single or multiple) extending into the renal collecting system; also main renal artery thrombosis from blunt trauma, segmental renal vein, or both; or artery injury with contained bleeding.

Grade V—Multiple grade IV parenchymal lacerations, renal pedicle avulsion, or both; main renal vein or artery injury from penetrating trauma; main renal artery or vein thrombosis.

B. Late Pathologic Findings (Figure 18–6)

1. Urinoma—Deep lacerations that are not repaired may result in persistent urinary extravasation and late complications of a large perinephric renal mass and, eventually, hydronephrosis and abscess formation.

2. Hydronephrosis—Large hematomas in the retroperitoneum and associated urinary extravasation may result in perinephric fibrosis engulfing the ureteropelvic junction, causing hydronephrosis. Follow-up excretory CT scan is indicated in all cases of high grade (VI-V) renal trauma after 48 hours.

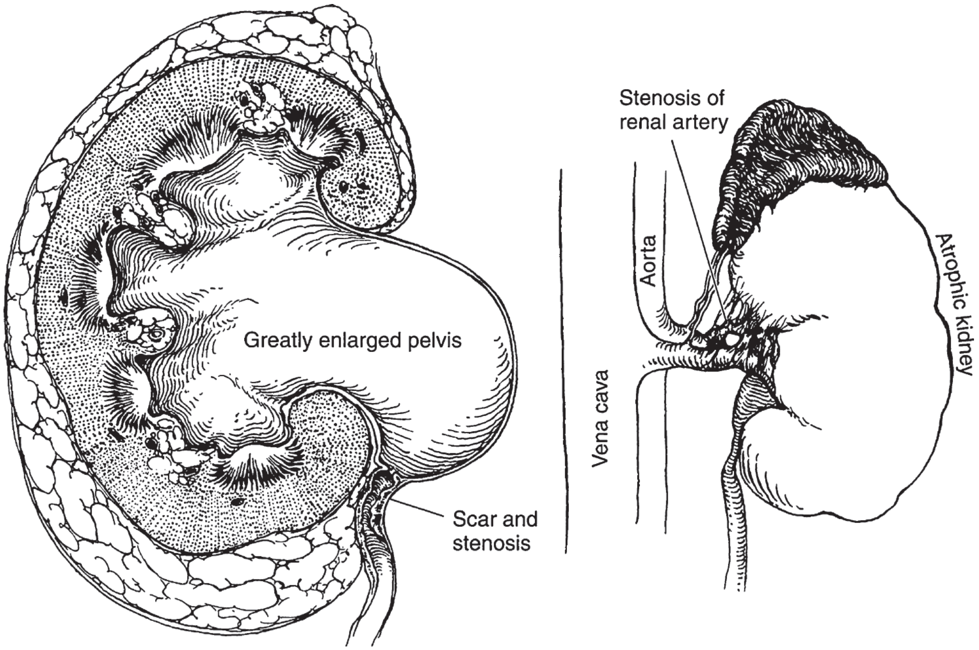
3. Arteriovenous fistula—Arteriovenous fistulas may occur after penetrating injuries but are not common.

4. Renal vascular hypertension—The blood flow in tissue rendered nonviable by injury is compromised; this results in renal vascular hypertension in <1% of cases. Fibrosis from surrounding trauma has also been reported to constrict the renal artery and cause renal hypertension.

Clinical Findings and Indications for Studies

Microscopic or gross hematuria following trauma to the abdomen indicates injury to the urinary tract. It bears repeating that stab or gunshot wounds to the flank area should alert the physician to possible renal injury regardless of whether hematuria is present. Some cases of renal vascular injury are not associated with hematuria. These cases are almost always due to rapid deceleration accidents and are an indication for imaging studies.

The degree of renal injury does not correspond to the degree of hematuria, since gross hematuria may occur in minor renal trauma and only mild hematuria in major trauma. However, not all adult patients sustaining blunt trauma require full imaging evaluation of the kidney (Figure 18–1). On the basis of findings in >1800 blunt renal trauma injuries, Miller and McAninch (1995) recommended that patients with gross hematuria or microscopic hematuria with shock (systolic



▲ **Figure 18–6.** Late pathologic findings in renal trauma. ***Left:*** Ureteropelvic stenosis with hydronephrosis secondary to fibrosis from extravasation of blood and urine. ***Right:*** Atrophy of kidney caused by injury (stenosis) of arterial blood supply.

blood pressure <90 mm Hg) undergo radiographic assessment while patients with microscopic hematuria without shock need not. However, should physical examination or associated injuries prompt reasonable suspicion of a renal injury, renal imaging should be undertaken. This is especially true of patients with rapid deceleration trauma, who may have renal injury without the presence of hematuria.

A. Symptoms

There is usually visible evidence of abdominal trauma. Pain may be localized to one flank area or over the abdomen. Associated injuries such as ruptured abdominal viscera or multiple pelvic fractures also cause acute abdominal pain and may obscure the presence of renal injury. Catheterization usually reveals hematuria. Retroperitoneal bleeding may cause abdominal distention, ileus, and nausea and vomiting.

B. Signs

Initially, shock or signs of a large loss of blood from heavy retroperitoneal bleeding may be noted. Ecchymosis in the flank or upper quadrants of the abdomen is often noted. Lower rib fractures are frequently found. Diffuse abdominal tenderness may be found on palpation; an "acute abdomen" usually indicates free blood in the peritoneal cavity. A palpable mass may represent a large retroperitoneal hematoma or perhaps urinary extravasation. If the retroperitoneum has been torn, free blood may be noted in the peritoneal cavity, but no palpable mass will be evident. The abdomen may be distended and bowel sounds absent.

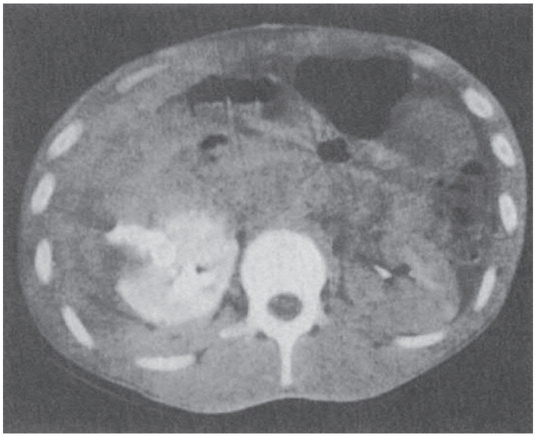
C. Laboratory Findings

Microscopic or gross hematuria is usually present. The hematocrit may be normal initially, but a drop may be found when serial studies are done. This finding represents persistent retroperitoneal bleeding and development of a large retroperitoneal hematoma. Persistent bleeding may necessitate intervention.

D. Staging and X-Ray Findings

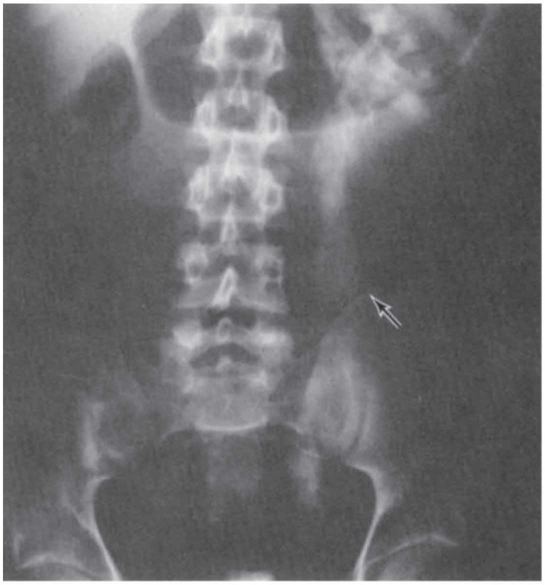
Staging of renal injuries allows a systematic approach to these problems (Figures 18–1 through 18–3). Adequate studies help define the extent of injury and dictate appropriate management. For example, blunt trauma to the abdomen associated with gross hematuria and a normal urogram requires no additional renal studies; however, nonvisualization of the kidney requires immediate arteriography or CT scan to determine whether renal vascular injury exists. Ultrasonography and retrograde urography are of little use initially in the evaluation of renal injuries.

Staging begins with an abdominal CT scan, the most direct and effective means of staging renal injuries. This noninvasive technique clearly defines parenchymal lacerations and urinary extravasation; shows the extent of the retroperitoneal hematoma; identifies nonviable tissue; and outlines injuries to surrounding organs such as the pancreas, spleen, liver, and bowel (Figure 18–7). (If CT scan is not available, an intravenous pyelogram can be obtained [Figure 18–8].)

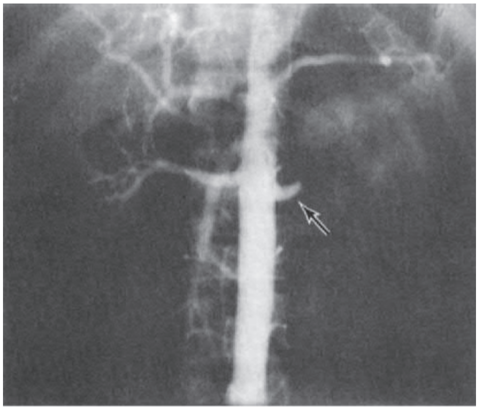


▲ **Figure 18–7.** Computed tomography scan of right kidney following knife stab wound. Laceration with urine extravasation is seen. Large right retroperitoneal hematoma is present.

Arteriography defines major arterial and parenchymal injuries when previous studies have not fully done so. Arterial thrombosis and avulsion of the renal pedicle are best



▲ **Figure 18–8.** Blunt renal trauma to left kidney demonstrating extravasation (at *arrow*) on intravenous urogram.



▲ **Figure 18–9.** Arteriogram following blunt abdominal trauma shows typical findings of acute renal artery thrombosis (*arrow*) of left kidney.

diagnosed by arteriography and are likely when the kidney is not visualized on imaging studies (Figure 18–9). The major causes of nonvisualization on an excretory urogram are total pedicle avulsion, arterial thrombosis, severe contusion causing vascular spasm, and absence of the kidney (either congenital or from operation).

Radionuclide renal scans have been used in staging renal trauma. However, in emergency management, this technique is less sensitive than arteriography or CT.

Differential Diagnosis

Trauma to the abdomen and flank areas is not always associated with renal injury. In such cases, there is no hematuria, and the results of imaging studies are normal.

Complications

A. Early Complications

Hemorrhage is perhaps the most important immediate complication of renal injury. Heavy retroperitoneal bleeding may result in rapid exsanguination. Patients must be observed closely, with careful monitoring of blood pressure and hematocrit. Complete staging must be done early (Figures 18–1 through 18–3). The size and expansion of palpable masses must be carefully monitored. Bleeding ceases spontaneously in 80–85% of cases. Persistent retroperitoneal bleeding or heavy gross hematuria may require early operation.

Urinary extravasation from renal fracture may show as an expanding mass (urinoma) in the retroperitoneum. These collections are prone to abscess formation and sepsis. A resolving retroperitoneal hematoma may cause slight fever (38.3°C [101°F]), but higher temperatures suggest infection. A perinephric abscess may form, resulting in abdominal tenderness and flank pain.

B. Late Complications

Hypertension, hydronephrosis, arteriovenous fistula, calculus formation, and pyelonephritis are important late complications. Careful monitoring of blood pressure for several years is necessary to watch for hypertension. Heavy late bleeding may occur 1–4 weeks after injury, which should prompt imaging to detect the source.

Treatment

A. Emergency Measures

The objectives of early management are prompt treatment of shock and hemorrhage, complete resuscitation, and evaluation of associated injuries.

B. Surgical Measures

1. Blunt injuries—Minor renal injuries from blunt trauma account for 85% of cases and do not usually require operation. Bleeding stops spontaneously with bed rest and hydration. Cases in which operation is indicated include those associated with persistent retroperitoneal bleeding, significant urinary extravasation, evidence of significant nonviable renal parenchyma, and renal pedicle injuries (<5% of all renal injuries). Aggressive preoperative staging allows complete definition of injury before operation.

2. Penetrating injuries—Penetrating injuries frequently require exploration. The exception to this rule is when staging has been complete and only minor parenchymal injury, with no urinary extravasation, is noted. In 80% of cases of penetrating injury, associated organ injury requires operation; thus, renal exploration is only an extension of this procedure.

C. Treatment of Complications

Retroperitoneal urinoma or perinephric abscess demands prompt surgical drainage. Malignant hypertension requires vascular repair or nephrectomy. Hydronephrosis may require surgical correction or nephrectomy.

Angioembolization done by interventional radiology provides excellent control of active bleeding from the kidney. This approach, in the trauma setting, is most often used when nonoperative management has been selected and renal parenchymal bleeding persists or develops after days or weeks of observation. In high-volume trauma centers, angioembolization can be utilized as an alternative to operative intervention to treat solitary high-grade renal trauma that does not respond to adequate resuscitation.

Prognosis

With careful follow-up, most renal injuries have an excellent prognosis, with spontaneous healing and return of renal function. Follow-up CT and renal scan and monitoring of blood pressure ensure detection and appropriate management of late hydronephrosis and hypertension.

INJURIES TO THE URETER

Ureteral injury is rare but may occur, usually during a difficult pelvic surgical procedure or as a result of stab or gunshot wounds. Rapid deceleration accidents may avulse the ureter from the renal pelvis. Endoscopic basket manipulation of ureteral calculi may result in injury.

Etiology

Large pelvic masses (benign or malignant) may displace the ureter laterally and engulf it in reactive fibrosis. This may lead to ureteral injury during dissection, since the organ is anatomically malpositioned. Inflammatory pelvic disorders may involve the ureter in a similar way. Extensive carcinoma of the colon may invade areas outside the colon wall and directly involve the ureter; thus, resection of the ureter may be required along with resection of the tumor mass. Devascularization may occur with extensive pelvic lymph node dissections or after radiation therapy to the pelvis for pelvic cancer. In these situations, ureteral fibrosis and subsequent stricture formation may develop along with ureteral fistulas. Endoscopic manipulation of a ureteral calculus with a stone basket or ureteroscope may result in ureteral perforation or avulsion.

Pathogenesis and Pathology

The ureter may be inadvertently ligated and cut during difficult pelvic surgery. In such cases, sepsis and severe renal damage usually occur postoperatively. If a partially divided ureter is unrecognized at operation, urinary extravasation and subsequent buildup of a large urinoma will ensue, which usually leads to ureterovaginal or ureterocutaneous fistula formation. Intraperitoneal extravasation of urine can also occur, causing ileus and peritonitis. After partial transection of the ureter, some degree of stenosis and reactive fibrosis develops, with concomitant mild-to-moderate hydronephrosis.

Clinical Findings

A. Symptoms

If the ureter has been completely or partially ligated during operation, the postoperative course is usually marked by fever of 38.3–38.8°C (101–102°F) as well as flank and lower quadrant pain. Such patients often experience paralytic ileus with nausea and vomiting. If ureterovaginal or cutaneous fistula develops, it usually does so within the first 10 postoperative days.

Ureteral injuries from external violence should be suspected in patients who have sustained stab or gunshot wounds to the retroperitoneum. The midportion of the ureter seems to be the most common site of penetrating injury. There are usually associated vascular and other abdominal visceral injuries.

B. Signs

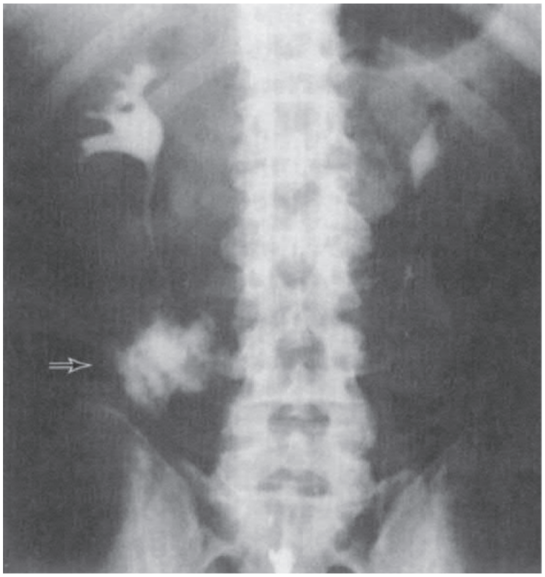
The acute hydronephrosis of a totally ligated ureter results in severe flank pain and abdominal pain with nausea and vomiting early in the postoperative course and with associated ileus. Signs and symptoms of acute peritonitis may be present if there is urinary extravasation into the peritoneal cavity. Watery discharge from the wound or vagina may be identified as urine by determining the creatinine concentration of a small sample—urine has many times the creatinine concentration found in serum—and by intravenous injection of 10 mL of indigo carmine, which will appear in the urine as dark blue.

C. Laboratory Findings

Ureteral injury from external violence is manifest by microscopic hematuria in 90% of cases. Urinalysis and other laboratory studies are of little use in diagnosis when injury has occurred from other causes.

D. Imaging Findings

Diagnosis is by excretory urography or delayed abdominal spiral CT scan. A plain film of the abdomen may demonstrate a large area of increased density in the pelvis or in an area of retroperitoneum where injury is suspected. After injection of contrast material, delayed excretion is noted with hydronephrosis. Partial transection of the ureter results in more rapid excretion, but persistent hydronephrosis is usually present, and contrast extravasation at the site of injury is noted on delayed films (Figure 18–10).



▲ **Figure 18–10.** Stab wound of right ureter shows extravasation (at *arrow*) on intravenous urogram.

In acute injury from external violence, the excretory urogram usually appears normal, with very mild fullness down to the point of extravasation at the ureteral transection.

Retrograde ureterography demonstrates the exact site of obstruction or extravasation.

E. Ultrasonography

Ultrasonography outlines hydroureter or urinary extravasation as it develops into a urinoma and can be used to rule out ureteral injury in the early postoperative period.

F. Radionuclide Scanning

Radionuclide scanning demonstrates delayed excretion on the injured side, with evidence of increasing counts owing to accumulation of urine in the renal pelvis. Its great benefit, however, is in the assessment of renal function after surgical correction.

Differential Diagnosis

Postoperative bowel obstruction and peritonitis may cause symptoms similar to those of acute ureteral obstruction from injury. Fever, "acute abdomen," and associated nausea and vomiting following difficult pelvic surgery are definite indications for screening sonography or excretory urography to establish whether ureteral injury has occurred.

Deep wound infection must be considered postoperatively in patients with fever, ileus, and localized tenderness. The same findings are consistent with urinary extravasation and urinoma formation.

Acute pyelonephritis in the early postoperative period may also result in findings similar to those of ureteral injury. Sonography shows normal results, and urography shows no evidence of obstruction.

Complications

Ureteral injury may be complicated by stricture formation with resulting hydronephrosis in the area of injury. Chronic urinary extravasation from unrecognized injury may lead to formation of a large retroperitoneal urinoma. Pyelonephritis from hydronephrosis and urinary infection may require prompt proximal drainage.

Treatment

Prompt treatment of ureteral injuries is required. The best opportunity for successful repair is in the operating room when the injury occurs. If the injury is not recognized until 7–10 days after the event and if no infection, abscess, or other complications exist, then immediate reexploration and repair are indicated. Proximal urinary drainage by percutaneous nephrostomy or formal nephrostomy should be considered if the injury is recognized late or if the patient has significant complications that make immediate reconstruction unsatisfactory. The goals of ureteral repair are to achieve complete debridement, a tension-free spatulated anastomosis, watertight closure, ureteral stenting (in selected cases), and retroperitoneal drainage.

A. Lower Ureteral Injuries

Injuries to the lower third of the ureter allow several options in management. The procedure of choice is reimplantation into the bladder combined with a psoas-hitch procedure to minimize tension on the ureteral anastomosis. Primary ureteroureterostomy can be used in lower-third injuries when the ureter has been ligated without transection. The ureter is usually long enough for this type of anastomosis. A bladder tube flap can be used when the ureter is shorter.

Transureteroureterostomy may be used in lower-third injuries if extensive urinoma and pelvic infection have developed. This procedure allows anastomosis and reconstruction in an area away from the pathologic processes.

B. Midureteral Injuries

Midureteral injuries usually result from external violence and are best repaired by primary ureteroureterostomy or transureteroureterostomy. Downward nephropexy may help relieve anastomotic tension.

C. Upper Ureteral Injuries

Injuries to the upper third of the ureter are best managed by primary ureteroureterostomy. If there is extensive loss of the ureter, autotransplantation of the kidney can be done as well as bowel replacement of the ureter.

D. Stenting

Most anastomoses after repair of ureteral injury should be stented. The preferred technique is to insert a silicone internal stent through the anastomosis before closure. These stents have a J-shape memory curve on each end to prevent their migration in the postoperative period. After 3–4 weeks of healing, stents can be endoscopically removed from the bladder. The advantages of internal stenting are maintenance of a straight ureter with a constant caliber during early healing, the presence of a conduit for urine during healing, prevention of urinary extravasation, maintenance of urinary diversion, and easy removal.

Prognosis

The prognosis for ureteral injury is excellent if the diagnosis is made early and prompt corrective surgery is done. Delay in diagnosis worsens the prognosis because of infection, hydronephrosis, abscess, and fistula formation.

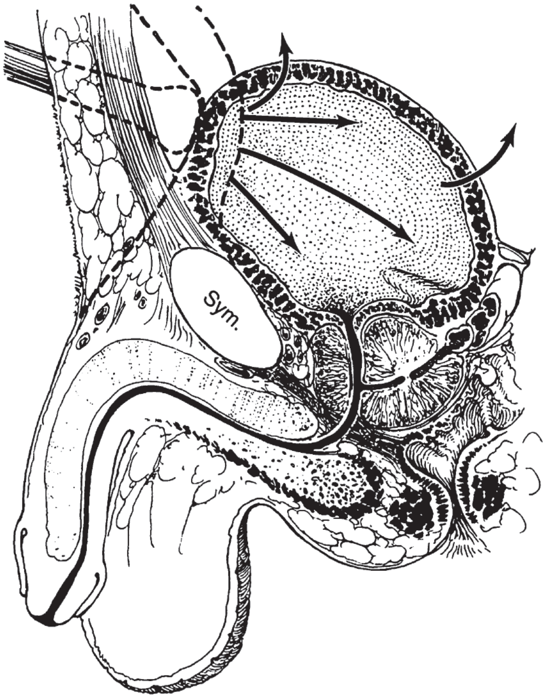
INJURIES TO THE BLADDER

Bladder injuries occur most often from external force and are often associated with pelvic fractures. (About 15% of all pelvic fractures are associated with concomitant bladder or urethral injuries.) Iatrogenic injury may result from gynecologic and other extensive pelvic procedures as well as from hernia repairs and transurethral operations.

Pathogenesis and Pathology (Figure 18–11)

The bony pelvis protects the urinary bladder very well. When the pelvis is fractured by blunt trauma, fragments from the fracture site may perforate the bladder. These perforations usually result in extraperitoneal rupture. If the urine is infected, extraperitoneal bladder perforations may result in deep pelvic abscess and severe pelvic inflammation.

When the bladder is filled to near capacity, a direct blow to the lower abdomen may result in bladder disruption. This type of disruption is ordinarily intraperitoneal. Since the reflection of the pelvic peritoneum covers the dome of the bladder, a linear laceration will allow urine to flow into the abdominal cavity. If the diagnosis is not established immediately and if the urine is sterile, no symptoms may be noted for several days. If the urine is infected, immediate peritonitis and acute abdomen will develop.



▲ Figure 18–11. Mechanism of vesical injury. A direct blow over the full bladder causes increased intravesical pressure. If the bladder ruptures, it will usually rupture into the peritoneal cavity.

Clinical Findings

Pelvic fracture accompanies bladder rupture in 90% of cases. The diagnosis of pelvic fracture can be made initially in the emergency room by lateral compression on the bony pelvis, since the fracture site will show crepitus and be painful to the touch.

A. Symptoms

There is usually a history of lower abdominal trauma. Blunt injury is the usual cause. Patients ordinarily are unable to urinate, but when spontaneous voiding occurs, gross hematuria is usually present. Most patients complain of pelvic or lower abdominal pain.

B. Signs

Heavy bleeding associated with pelvic fracture may result in hemorrhagic shock, usually from venous disruption of pelvic vessels. Evidence of external injury from a gunshot or stab wound in the lower abdomen should make one suspect bladder injury, manifest by marked tenderness of the suprapubic area and lower abdomen. An acute abdomen may occur with intraperitoneal bladder rupture. On rectal examination, landmarks may be indistinct because of a large pelvic hematoma.

C. Laboratory Findings

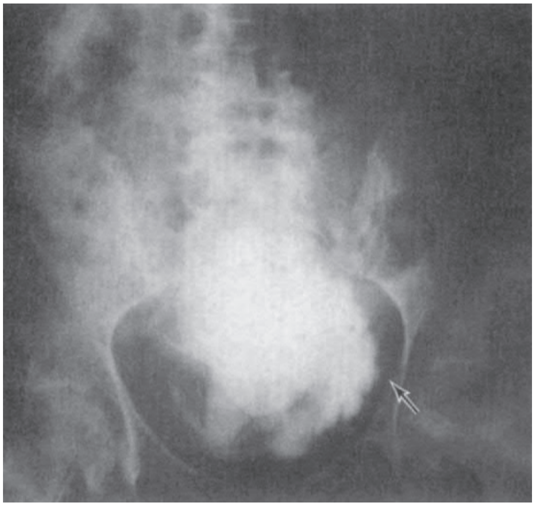
Catheterization usually is required in patients with pelvic trauma, but not if bloody urethral discharge is noted. Bloody urethral discharge indicates urethral injury, and a urethrogram is necessary before catheterization (Figures 18–1 through 18–3). When catheterization is done, gross or, less commonly, microscopic hematuria is usually present. Urine taken from the bladder at the initial catheterization should be cultured to determine whether infection is present.

D. X-Ray Findings

A plain abdominal film generally demonstrates pelvic fractures. There may be haziness over the lower abdomen from blood and urine extravasation. A CT scan should be obtained to establish whether kidney and ureteral injuries are present.

Bladder disruption is shown on cystography. The bladder should be filled with 300 mL of contrast material and a plain film of the lower abdomen obtained. Contrast medium should be allowed to drain out completely, and a second film of the abdomen should be obtained. The drainage film is extremely important, because it demonstrates areas of extraperitoneal extravasation of blood and urine that may not appear on the filling film (Figure 18–12). With intraperitoneal extravasation, free contrast medium is visualized in the abdomen, highlighting bowel loops (Figure 18–13).

Computed tomographic cystography is an excellent method for detecting bladder rupture; however, retrograde filling of the bladder with 300 mL of contrast medium is necessary to distend the bladder completely. Incomplete distention

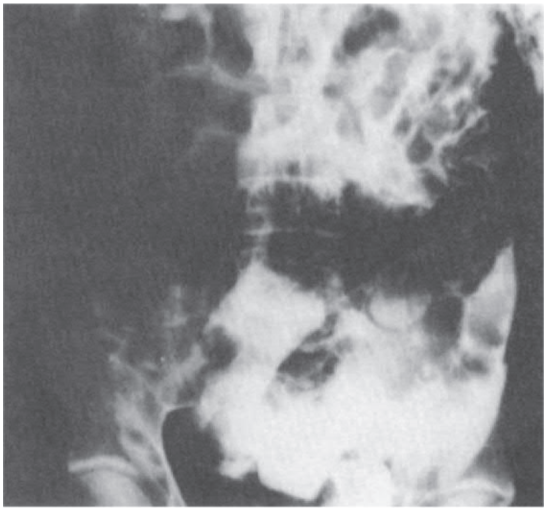


▲ **Figure 18–12.** Extraperitoneal bladder rupture. Extravasation (at *arrow*) seen outside the bladder in the pelvis on cystogram.

with consequent missed diagnosis of bladder rupture often occurs when the urethral catheter is clamped during standard abdominal CT scan with intravenous contrast injection.

Complications

A pelvic abscess may develop from extraperitoneal bladder rupture; if the urine becomes infected, the pelvic hematoma becomes infected also. Intraperitoneal bladder rupture with extravasation of urine into the abdominal cavity causes delayed peritonitis. Partial incontinence may result from bladder injury when the laceration extends into the bladder neck. Meticulous repair may ensure normal urinary control.



▲ **Figure 18–13.** Intraperitoneal bladder rupture. Cystogram shows contrast surrounding loops of bowel.

Treatment

A. Emergency Measures

Shock and hemorrhage should be treated.

B. Surgical Measures

A lower midline abdominal incision should be made. As the bladder is approached in the midline, a pelvic hematoma, which is usually lateral, should be avoided. Entering the pelvic hematoma can result in increased bleeding from release of tamponade and in infection of the hematoma, with subsequent pelvic abscess. The bladder should be opened in the midline and carefully inspected. After repair, a urethral catheter is typically used in favor of a suprapubic tube. In cases of a permanent spinal injury, a suprapubic catheter is preferred and should exit the extraperitoneal position.

1. Extraperitoneal bladder rupture—Extraperitoneal bladder rupture can be successfully managed with urethral catheter drainage only. (Typically, 10 days will provide adequate healing time.) Large blood clots or bone spicules in the bladder or injuries involving the bladder neck should be managed surgically.

As the bladder is opened in the midline, it should be carefully inspected and lacerations closed from within. Polyglycolic acid or chromic absorbable sutures should be used.

Extraperitoneal bladder lacerations occasionally extend into the bladder neck and should be repaired meticulously. Fine absorbable sutures should be used to ensure complete reconstruction so that the patient will have urinary control after injury. Such injuries are best managed with indwelling urethral catheterization.

2. Intraperitoneal rupture—Intraperitoneal bladder ruptures should be repaired via a transperitoneal approach after careful transvesical inspection and closure of any other perforations. The peritoneum must be closed carefully over the area of injury. The bladder is then closed in separate layers by absorbable suture. All extravasated fluid from the peritoneal cavity should be removed before closure.

3. Pelvic fracture—Stable fracture of the pubic rami is usually present. In such cases, the patient can be ambulatory within 4–5 days without damage or difficulty. Unstable pelvic fractures requiring external fixation have a more protracted course.

4. Pelvic hematoma—There may be heavy uncontrolled bleeding from rupture of pelvic vessels even if the hematoma has not been entered at operation. At exploration and bladder repair, packing the pelvis with laparotomy tapes often controls the problem. If bleeding persists, it may be necessary to leave the tapes in place for 24 hours and operate again to remove them. Angioembolization of pelvic vessels is useful in controlling persistent pelvic bleeding.

Prognosis

With appropriate treatment, the prognosis is excellent. The suprapubic cystostomy tube can be removed within 10 days, and the patient can usually void normally. Patients with lacerations extending into the bladder neck area may be temporarily incontinent, but full control is usually regained.

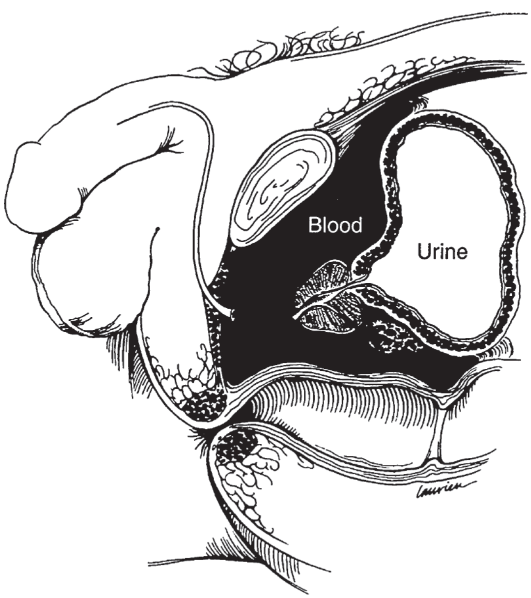
INJURIES TO THE URETHRA (GENERAL)

Urethral injuries are uncommon and occur most often in men, usually associated with pelvic fractures or straddle-type falls. They are rare in women. Various parts of the urethra may be lacerated, transected, or contused. Management varies according to the level of injury. The urethra can be separated into two broad anatomic divisions: the posterior urethra, consisting of the prostatic and membranous portions, and the anterior urethra, consisting of the bulbous and pendulous portions.

INJURIES TO THE POSTERIOR URETHRA

Etiology (Figure 18–14)

The membranous urethra passes through the pelvic floor and voluntary urinary sphincter and is the portion of the posterior urethra most likely to be injured. When pelvic fractures occur from blunt trauma, the membranous urethra is sheared from the prostatic apex at the prostatomembranous junction. The urethra can be transected by the same mechanism at the interior surface of the membranous urethra.



▲ **Figure 18–14.** Injury to the posterior (membranous) urethra. The prostate has been avulsed from the membranous urethra secondary to fracture of the pelvis. Extravasation occurs above the triangular ligament and is periprostatic and perivesical.

Clinical Findings

A. Symptoms

Patients usually complain of lower abdominal pain and inability to urinate. A history of crushing injury to the pelvis is usually obtained.

B. Signs

Blood at the urethral meatus is the single most important sign of urethral injury. The importance of this finding cannot be overemphasized, because an attempt to pass a urethral catheter may result in infection of the periprostatic and perivesical hematoma and conversion of an incomplete laceration to a complete one. The presence of blood at the external urethral meatus indicates that immediate urethrography is necessary to establish the diagnosis.

Suprapubic tenderness and the presence of pelvic fracture are noted on physical examination. A large developing pelvic hematoma may be palpated. Perineal or suprapubic contusions are often noted. Rectal examination may reveal a large pelvic hematoma with the prostate displaced superiorly. Rectal examination can be misleading, however, because a tense pelvic hematoma may resemble the prostate on palpation. Superior displacement of the prostate does not occur if the puboprostatic ligaments remain intact. Partial disruption of the membranous urethra (currently 10% of cases) is not accompanied by prostatic displacement.

C. X-Ray Findings

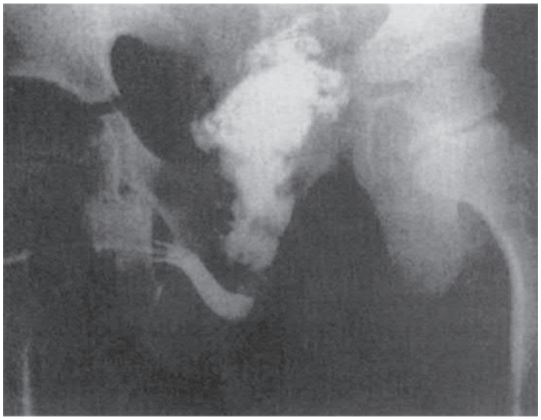
Fractures of the bony pelvis are usually present. A urethrogram (using 20–30 mL of water-soluble contrast material) shows the site of extravasation at the prostatomembranous junction. Ordinarily, there is free extravasation of contrast material into the perivesical space (Figure 18–15). Incomplete prostatomembranous disruption is seen as minor extravasation, with a portion of contrast material passing into the prostatic urethra and bladder.

D. Instrumental Examination

The only instrumentation involved should be for urethrography. Catheterization or urethroscopy should not be done, because these procedures pose an increased risk of hematoma, infection, and further damage to partial urethral disruptions.

Differential Diagnosis

Bladder rupture may be associated with posterior urethral injuries in approximately 20% of cases. Cystography cannot be done preoperatively, since a urethral catheter should not be passed. Careful evaluation of the bladder at operation is necessary.



▲ **Figure 18–15.** Ruptured prostatomembranous urethra shows free extravasation on urethrogram. No contrast medium is seen entering the prostatic urethra.

▶ Complications

Stricture, impotence, and incontinence as complications of prostatomembranous disruption are among the most severe and debilitating mishaps that result from trauma to the urinary system. Stricture following primary repair and anastomosis occurs in about 50% of cases.

The incidence of impotence after primary repair is 30–80% (mean, about 50%). This figure can be reduced to 30–35% by suprapubic drainage with delayed urethral reconstruction.

Total urinary incontinence occurs in <2% of patients and is typically associated with severe sacral fracture and S2–S4 nerve injury.

▶ Treatment

A. Emergency Measures

Shock and hemorrhage should be treated.

B. Surgical Measures

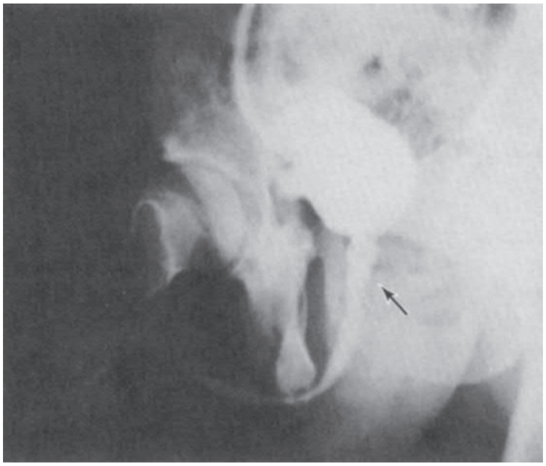
Urethral catheterization should be avoided.

1. Immediate management—Initial management should consist of suprapubic cystostomy to provide urinary drainage. A midline lower abdominal incision should be made, with caution exercised to avoid the large pelvic hematoma. The bladder and prostate are usually elevated superiorly by large periprostatic and perivesical hematomas. The bladder often is distended by a large volume of urine accumulated during the period of resuscitation and operative preparation. The urine is often clear and free of blood, but gross hematuria may be present. The bladder should be opened in the midline and carefully inspected for lacerations. If a laceration is present, the bladder should be closed with absorbable suture material and a cystostomy tube inserted for urinary drainage. This approach involves no urethral instrumentation or manipulation. The suprapubic cystostomy is maintained in place for about 3 months. This allows resolution of the pelvic hematoma, and the prostate and bladder will slowly return to their anatomic positions.

Incomplete laceration of the posterior urethra heals spontaneously, and the suprapubic cystostomy can be removed within 2–3 weeks. The cystostomy tube should not be removed before voiding cystourethrography shows that no extravasation persists.

2. Delayed urethral reconstruction—Reconstruction of the urethra after prostatic disruption can be undertaken within 3 months, assuming that there is no pelvic abscess or other evidence of persistent pelvic infection. Before reconstruction, a combined cystogram and urethrogram should be done to determine the exact length of the resulting urethral stricture. This stricture usually is 1–2 cm long and situated immediately posterior to the pubic bone. The preferred approach is a single-stage reconstruction of the urethral rupture defect with direct excision of the strictured area and anastomosis of the bulbous urethra directly to the apex of the prostate. A 16Fr silicone urethral catheter should be left in place along with a suprapubic cystostomy. Catheters are removed within a month, and the patient is then able to void (Figure 18–16).

3. Immediate urethral realignment—Some surgeons prefer to perform primary endoscopic realignment of the urethra within 7 days of injury after the patient has been stabilized. Prolonged attempts at realignment (>45 minutes) must be avoided as fluid extravasation leads to scarring, erectile dysfunction, and incontinence. Whether to perform primary endoscopic realignment or suprapubic tube placement and delayed repair is an area of



▲ **Figure 18–16.** Delayed repair of urethral injury. Normal voiding urethrogram after transpubic repair of stricture following prostatomembranous urethral disruption. *Arrow* indicates area of repair.

great controversy in reconstructive urology with ardent supporters on both sides.

C. General Measures

After delayed reconstruction by a perineal approach, patients are allowed ambulation on the first postoperative day and usually can be discharged within 3 days.

D. Treatment of Complications

Approximately 1 month after the delayed reconstruction, the urethral catheter can be removed and a voiding cystogram obtained through the suprapubic cystostomy tube. If the cystogram shows a patent area of reconstruction free of extravasation, the suprapubic catheter can be removed; if there is extravasation or stricture, suprapubic cystostomy should be maintained. A follow-up urethrogram should be obtained within 2 months to watch for stricture development.

Stricture, if present (<5%), is usually very short, and urethrotomy under direct vision offers easy and rapid cure. The patient may be impotent for several months after delayed repair. Impotence is permanent in about 10% of patients. Implantation of a penile prosthesis is indicated if impotence is still present 2 years after reconstruction (see Chapter 38). Incontinence after posterior urethral rupture and delayed repair is rare (<2%) and is usually related to the extent of injury rather than to the repair.

Prognosis

If complications can be avoided, the prognosis is excellent. Urinary infections ultimately resolve with appropriate management.

INJURIES TO THE ANTERIOR URETHRA

Etiology (Figure 18–17)

The anterior urethra is the portion distal to the urogenital diaphragm. Straddle injury may cause laceration or contusion of the urethra. Self-instrumentation or iatrogenic instrumentation may cause partial disruption.

Pathogenesis and Pathology

A. Contusion

Contusion of the urethra is a sign of crush injury without urethral disruption. Perineal hematoma usually resolves without complications.

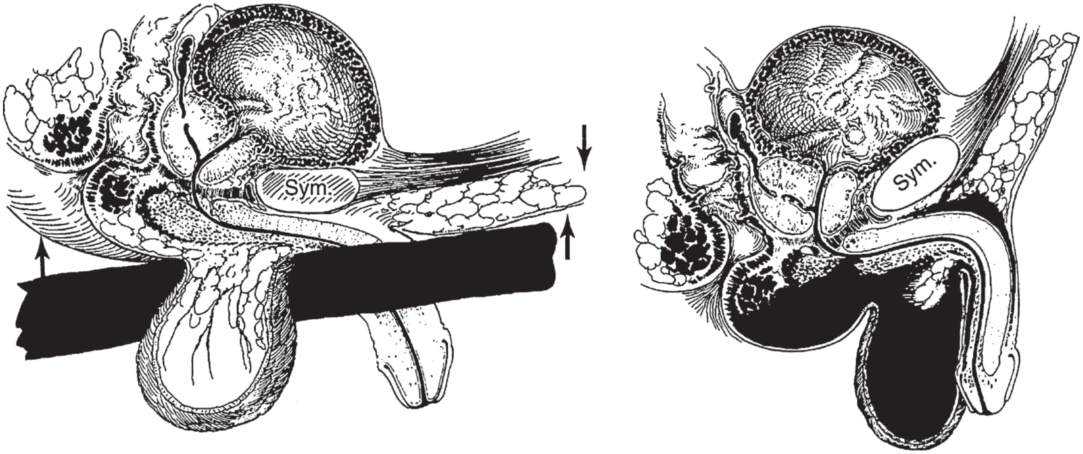
B. Laceration

A severe straddle injury may result in laceration of part of the urethral wall, allowing extravasation of urine. If the extravasation is unrecognized, it may extend into the scrotum, along the penile shaft, and up to the abdominal wall. It is limited only by Colles' fascia and often results in sepsis, infection, and serious morbidity.

Clinical Findings

A. Symptoms

There is usually a history of a fall, and in some cases, a history of instrumentation. Bleeding from the urethra is usually present. There is local pain into the perineum and sometimes massive perineal hematoma. If voiding has occurred and extravasation is noted, sudden swelling in the area will be present. If diagnosis has been delayed, sepsis and severe infection may be present.



▲ **Figure 18–17.** Injury to the bulbous urethra. ***Left:*** Mechanism: Usually a perineal blow or fall astride an object; crushing of urethra against inferior edge of pubic symphysis. ***Right:*** Extravasation of blood and urine enclosed within Colles' fascia (see Figures 18–1 through 18–9).

B. Signs

The perineum is very tender; a mass may be found, as may blood at the urethral meatus. Rectal examination reveals a normal prostate. The patient usually has a desire to void, but voiding should not be allowed until assessment of the urethra is complete. No attempt should be made to pass a urethral catheter, but if the patient's bladder is overdistended, percutaneous suprapubic cystostomy can be done as a temporary procedure.

When presentation of such injuries is delayed, there is massive urinary extravasation and infection in the perineum and the scrotum. The lower abdominal wall may also be involved. The skin is usually swollen and discolored.

C. Laboratory Findings

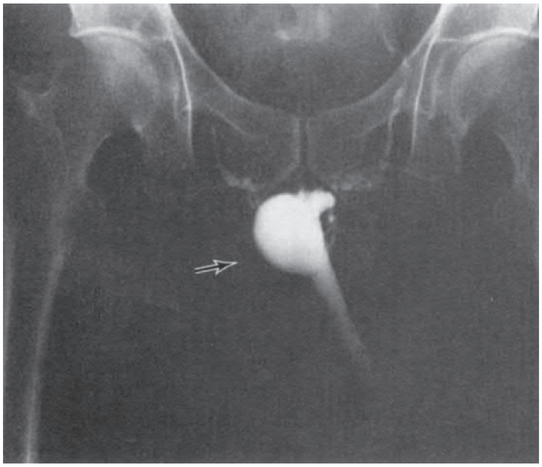
Blood loss seldom is excessive, particularly if secondary injury has occurred. The white count may be elevated with infection.

D. X-Ray Findings

A urethrogram, with instillation of 15–20 mL of water-soluble contrast material, demonstrates extravasation and the location of injury (Figure 18–18). A contused urethra shows no evidence of extravasation.

▶ Complications

Heavy bleeding from the corpus spongiosum injury may occur in the perineum as well as through the urethral meatus. Pressure applied to the perineum over the site of the injury usually controls bleeding. If hemorrhage cannot be controlled, immediate operation is required.



▲ **Figure 18–18.** Ruptured bulbar (anterior) urethra following straddle injury. Extravasation (at *arrow*) on urethrogram.

The complications of urinary extravasation are chiefly sepsis and infection. Aggressive debridement and drainage are required if there is infection. Stricture at the site of injury is a common complication, but surgical reconstruction may not be required unless the stricture significantly reduces urinary flow rates.

▶ Treatment

A. General

Major blood loss rarely occurs as a result of straddle injury. If heavy bleeding does occur, local pressure for control, followed by resuscitation, is required.

B. Specific Measures

1. Urethral contusion—The patient with urethral contusion shows no evidence of extravasation, and the urethra remains intact. After urethrography, the patient is allowed to void, and if the voiding occurs normally, without pain or bleeding, no additional treatment is necessary. If bleeding persists, urethral catheter drainage can be performed.

2. Urethral lacerations—Instrumentation of the urethra following urethrography should be avoided. A small midline incision in the suprapubic area readily exposes the dome of the bladder so that a suprapubic cystostomy tube can be inserted, allowing complete urinary diversion while the urethral laceration heals. Percutaneous cystostomy may also be used in such injuries. If only minor extravasation is noted on the urethrogram, a voiding study can be performed within 7 days after suprapubic catheter drainage to search for extravasation. In more extensive injuries, one should wait 2–3 weeks before doing a voiding study through the suprapubic catheter. Healing at the site of injury may result in stricture formation. Most of these strictures are not severe and do not require surgical reconstruction. The suprapubic cystostomy catheter may be removed if no extravasation is documented. Follow-up with documentation of urinary flow rates will show whether there is urethral obstruction from stricture.

3. Urethral laceration with extensive urinary extravasation—After major laceration, urinary extravasation may involve the perineum, scrotum, and lower abdomen. Drainage of these areas is indicated. Suprapubic cystostomy for urinary diversion is required. Infection and abscess formation are common and require antibiotic therapy.

4. Immediate repair—Immediate repair of urethral lacerations can be performed, but the procedure is difficult, and the incidence of associated stricture is high.

C. Treatment of Complications

Strictures at the site of injury may be extensive and require delayed reconstruction.

Prognosis

Urethral stricture is a major complication but, in most cases, does not require surgical reconstruction. If, when stricture resolves, urinary flow rates are poor and urinary infection and urethral fistula are present, reconstruction is required.

INJURIES TO THE PENIS

Disruption of the tunica albuginea of the penis (penile fracture) can occur during sexual intercourse. At presentation, the patient has penile pain and hematoma. This injury should be surgically corrected.

Gangrene and urethral injury may be caused by obstructing rings placed around the base of the penis. These objects must be removed without causing further damage. Penile amputation is seen occasionally, and in a few patients, the penis can be surgically replaced successfully by microsurgical techniques.

Total avulsion of the penile skin occurs from machinery injuries. Immediate debridement and skin grafting are usually successful in salvage. Injuries to the penis should suggest possible urethral damage, which should be investigated by urethrography.

INJURIES TO THE SCROTUM

Superficial lacerations of the scrotum may be debrided and closed primarily. Blunt trauma may cause local hematoma and ecchymosis, but these injuries resolve without difficulty. One must be certain that testicular rupture has not occurred.

Total avulsion of the scrotal skin may be caused by machinery accidents or other major trauma. The testes and spermatic cords are usually intact. It is important to provide coverage for these structures; this is best done by immediate surgical debridement and by placing the testes and spermatic cords in the subcutaneous tissues of the upper thighs. Later reconstruction of the scrotum can be done with a skin graft or thigh flap.

INJURIES TO THE TESTIS

Blunt trauma to the testis causes severe pain and, often, nausea and vomiting. Lower abdominal tenderness may be present. A hematoma may surround the testis and make delineation of its margin difficult. Ultrasonography can be used as an aid to better define the organ. If rupture has occurred, the sonogram will delineate the injury, which should be surgically repaired.

BIBLIOGRAPHY

Emergency Diagnosis and Management

Brandes S et al: Consensus on genitourinary trauma. BJU Int 2004;94:277.

Demetriades D et al: Pelvic fractures: Epidemiology and predictors of associated abdominal injuries. J Am Coll Surg 2002;195(1):1.

Morey AF et al: Consensus on genitourinary trauma. BJU Int 2004;94:507.

Rosenstein D, McAninch JW: Urologic emergencies. Med Clin North Am 2004;88:495.

Tarman GJ et al: Lower genitourinary injury and pelvic fractures in pediatric patients. Urology 2002;59:123.

Titton RL et al: Urine leaks and urinomas: Diagnosis and imaging-guided intervention. Radiographics 2003;23:1133.

Yossepowitch O et al: Urological injuries during cesarean section: Intraoperative diagnosis and management. J Urol 2004;172:196.

Ziran BH et al: Delays and difficulties in the diagnosis of lower urologic injuries in the context of pelvic fractures. J Trauma 2005;58:533.

Injuries to the Kidney

Armenakas NA et al: Indications for nonoperative management of renal stab wounds. J Urol 1999;161:768.

Barsness KA et al: Renovascular injury: An argument for renal preservation. J Trauma 2004;57:310.

Buckley JC, McAninch JW: Pediatric renal injuries. J Urol 2004; 172:687.

Buckley JC, McAninch JW: Revision of current American Association for the Surgery of Trauma Renal Injury grading system. J Trauma 2011;70(1):35–37.

Elliott SP et al: Renal arterial injuries: Single center analysis of management strategies and outcomes. J Urol 2007;178(6):2451–2455.

Johnson B et al: A need for reevaluation of sports participation recommendations for children with a solitary kidney. J Urol 2005; 174:686.

Knudson MM et al: Outcome after major renovascular injuries: A Western Trauma Association multicenter report. J Trauma 2000;49:1116.

McAninch JW et al: Renal reconstruction after injury. J Urol 1991; 145:932.

Miller KS, McAninch JW: Radiographic assessment of renal trauma: Our 15-year experience. J Urol 1995;154:352.

Morey AF et al: Urotrauma: AUA guideline. J Urol 2014;192(2):327–335.

Santucci RA et al: Evaluation and management of renal injuries: Consensus statement of renal trauma subcommittee. BJU Int 2004;93:937.

Santucci RA, Fisher MB: The literature increasingly supports expectant (conservative) management of renal trauma—a systematic review. J Trauma 2005;59:493.

Tasian GE et al: Evaluation of renal function after major renal injury: Correlation with the American Association for the Surgery of Trauma Injury Scale. J Urol 2010;183(1):196–200.

Voelzke BB, McAninch JW: The current management of renal trauma. Am Surg 2008;74(8):667–678.

Voelzke BB, McAninch JW: Renal gunshot wounds: Clinical management and outcome. J Trauma 2009;66(3):593–600.

Wessells H et al: Criteria for nonoperative treatment of significant penetrating renal lacerations. J Urol 1996;157:24.

Injuries to the Ureter

Elliott SP, McAninch JW: Ureteral injuries from external violence: The 25-year experience at San Francisco General Hospital. J Urol 2003;170:1213.

Zaid UB et al: Penetrating trauma to the ureter, bladder, and urethra. Curr Trauma Rep 2015;1(2):119-124 (epub 4/14/15).

Injuries to the Bladder

Elliott SP, McAninch JW: Extraperitoneal bladder trauma: Delayed surgical management can lead to prolonged convalescence. J Trauma 2009;66(1):274–275.

Gomez RG et al: Consensus statement on bladder injuries. BJU Int 2004;94:27.

Power N et al: Computed tomographic cystography in bladder trauma: Pictorial essay. Can Assoc Radiol J 2004;55(5):304.

Injuries to the Urethra

Alwaal A1 et al: The incidence, causes, mechanism, risk factors, classification, and diagnosis of pelvic fracture urethral injury. Arab J Urol 2015;13(1):2–6.

Chapple C et al: Consensus statement on urethral trauma. BJU Int 2004;93:1195.

Koraitim MM: On the art of anastomotic posterior urethroplasty: A 27-year experience. J Urol 2005;173:135.

McAninch JW, Voelzke BB: Managing urethral trauma in children. US Pediatr 2008;4(1):85–88.

Myers JB, McAninch JW: Management of posterior urethral disruption injuries. Nat Clin Pract Urol 2009;6:154–163.

Park S, McAninch JW: Straddle injuries to the bulbar urethra: Management and outcomes in 78 patients. J Urol 2004;171(Suppl 2, Pt 1): 722.

Yu NC et al: Fistulas of the genitourinary tract: A radiologic review. Radiographics 2004;24(5):1331.

Injuries to the Penis

Gomes CM et al: Genital trauma due to animal bites. J Urol 2001;165:80.

Mydlo JH: Surgeon experience with penile fracture. J Urol 2001; 166:526.

Zargooshi J: Penile fracture in Kermanshah, Iran: Report of 172 cases. J Urol 2000;164:364.

Injuries to the Scrotum

Buckley JC, McAninch JW: Use of ultrasonography in diagnosis of testicular injuries in blunt scrotal trauma. J Urol 2006;175:175.

Mohr AM et al: Management of trauma to the male external genitalia: The usefulness of American Association for the Surgery of Trauma organ injury scales. J Urol 2003;170:2311.

This page intentionally left blank

19

Urothelial Carcinoma: Cancers of the Bladder, Ureter, and Renal Pelvis

Badrinath R. Konety, MD, MBA; &
Peter R. Carroll, MD, MPH

BLADDER CARCINOMAS

Incidence

Bladder cancer is the second most common cancer of the genitourinary tract. It accounts for 7% of new cancer cases in men and 2% of new cancer cases in women. The incidence is higher in whites than in African-Americans, and there is a positive social class gradient for bladder cancer in both sexes. The average age at diagnosis is 65 years. By that age, approximately 75% of bladder cancers are localized to the bladder; 25% will have spread to regional lymph nodes or distant sites.

Risk Factors and Pathogenesis

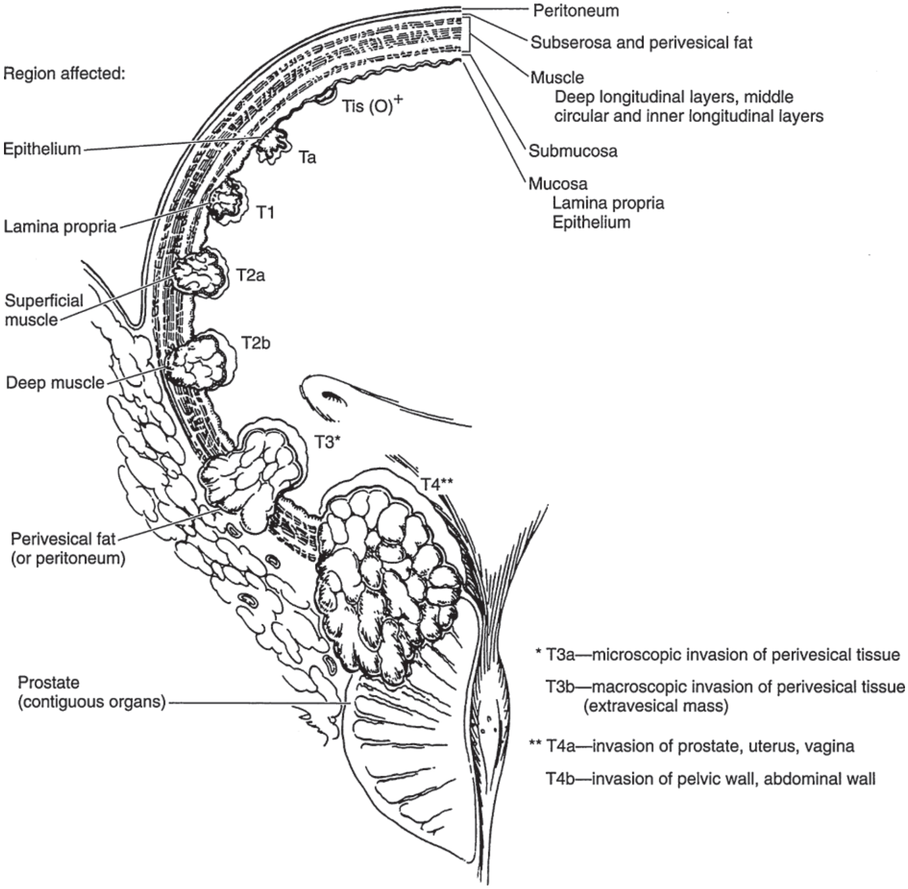
Cigarette smoking accounts for 65% of cases in men and 20–30% in women. In general, smokers have approximately a two- to threefold greater risk of bladder cancer than nonsmokers, and the association appears to be dose-related. The causative agents are thought to be α- and β-naphthylamine, which are secreted into the urine of smokers. The risk of bladder cancer appears to decrease after smoking cessation but may not reach the levels of never smokers.

Occupational exposure accounts for 15–35% of cases in men and 1–6% in women (Matanoski and Elliott, 1981). Workers in the chemical, dye, rubber, petroleum, leather, and printing industries are at increased risk. Specific occupational carcinogens include benzidine, β-naphthylamine, and 4-aminobiphenyl, and the latency period between exposure and tumor development may be prolonged. Patients who have received cyclophosphamide (Cytoxan) for the management of various malignant diseases are also at increased risk (Fairchild et al, 1979). Ingestion of artificial sweeteners has been proposed to be a risk factor, but several studies have failed to confirm any association (Elcock and Morgan, 1993). Physical trauma to the urothelium induced by infection, instrumentation, and calculi increases the risk of malignancy (Hicks, 1982). Arsenic in drinking water has also been implicated as a causative agent for bladder cancer, and high levels of exposure are associated with a doubling of the risk of bladder cancer (Saint-Jacques et al, 2014).

The exact genetic events leading to the development of bladder cancer are unknown, but they are likely to be multiple and may involve the activation of oncogenes and inactivation or loss of tumor suppressor genes (Olumi et al, 1990). Loss of genetic material on chromosome 9 appears to be a consistent finding in patients with low-grade, low-stage and high-grade, high-stage disease (Miyao et al, 1993; Tsai et al, 1990), which suggests that this may be an early event in bladder cancer development. Loss of chromosome 9 in multiple tumors from an individual patient supports the concept that genetic changes in bladder cancer represent a “field defect” that may occur throughout the urothelium. Studies examining p53 tumor suppressor gene mutations in primary, recurrent, and upper tract tumors suggest that these tumors can have a single clonal origin (Dalbagni et al, 2001; Sidransky et al, 1991). Additional genetic changes have been described that are specific for invasive bladder tumors. Chromosome 11p, which contains the c-Ha-ras proto-oncogene, is deleted in approximately 40% of bladder cancers (Olumi et al, 1990). Increased expression of the c-Ha-ras protein product, p21, has been detected in dysplastic and high-grade tumors but not in low-grade bladder cancers. Deletions of chromosome 17p have also been detected in over 60% of all invasive bladder cancers, but 17p deletions have not been described in superficial tumors. This finding is noteworthy because the p53 tumor suppressor gene maps to chromosome 17p. *TP53* alterations represent the most commonly identified genetic abnormality in human cancers, making deletion of this chromosome an important finding in carcinoma in situ (CIS) and muscle invasive bladder cancer. Mutations of the fibroblast growth factor receptor 3 (FGFr3) are found in >60% of papillomas and low-grade bladder tumors, and hence it is considered an oncogene. Ras mutations are also found in both low- and high-grade or muscle invasive tumors but Ras and FGFr3 mutations appear to be mutually exclusive (Jebar et al, 2005) and both are involved in activation of the MAP Kinase pathway. P53 mutations are less common in low-grade tumors and loss of FGFr3 with increased expression of p53 has been associated with higher stage and grade (Knowles, 2007). On the basis of comprehensive genomic analysis, muscle-invasive bladder cancers appear to have a high mutation rate. Commonly mutated genes include TERT, KDM6A, ERCC2, ERBB2, TP53, RB1, and FGFR3 (Cancer Genome Atlas Research Network, 2014; Robertson et al, 2017). Some mutations such as ERCC2 are more commonly identified in smokers. The ERCC2 gene expression has also been correlated with responsiveness to chemotherapy with platinum-based agents. In general, bladder cancers that have a "luminal" profile suggesting an origin from the luminal cells tend to be papillary in morphology and have a better prognosis. Cancers that have a "basal" profile indicating a basal cell origin tend to have a worse prognosis. The latter also have a genotype resembling squamous cell carcinomas. By grouping tumors by genes that are consistently over or under expressed, four or five broad categories of muscle invasive bladder cancer have been defined. These groupings are termed "clusters." They are also termed **basal**, **basal-claudin low**, **luminal**, and **luminal infiltrative** (Choi et al, 2014). A fifth cluster, which has a neuronal marker profile, has also been defined (Robertson et al, 2017). Basal tumors appear to be more responsive to chemotherapy, while tumors with a luminal profile have the best prognosis (Seiler et al, 2017). Such genetic analysis is increasingly being incorporated into evaluation and decision making regarding chemotherapy. Analysis of specific genetic abnormalities such as DNA repair genes may be a cost-effective way to predict response to neoadjuvant chemotherapy (Lotan et al, 2018).

Staging

The T staging system is depicted in Figure 19–1 and summarized in Table 19–1 (American Joint Committee on Cancer, 2017). Staging errors exist when one compares the clinical stage (that based on physical examination and imaging) with


Region affected:
Epithelium
Lamina propria
Superficial muscle
Deep muscle
Perivesical fat (or peritoneum)
Prostate (contiguous organs)
Tis (O)+
Ta
T1
T2a
T2b
T3*
T4**
Peritoneum
Subserosa and perivesical fat
Muscle
Deep longitudinal layers, middle circular and inner longitudinal layers
Submucosa
Mucosa
Lamina propria
Epithelium

* T3a—microscopic invasion of perivesical tissue

T3b—macroscopic invasion of perivesical tissue (extravesical mass)

** T4a—invasion of prostate, uterus, vagina

T4b—invasion of pelvic wall, abdominal wall

▲ **Figure 19–1.** Staging of bladder cancer.

Table 19–1. TNM staging of bladder cancer.

T category	Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades (any of): prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades directly into prostatic stroma, uterus, vagina
T4b	Extravesical tumor invades pelvic wall or abdominal wall
Lymph nodes	
N category	**Criteria**
NX	Lymph nodes cannot be assessed
N0	No lymph node metastases
N1	Single regional lymph node metastases in true pelvis (perivesical, obturator, internal and external iliac, sacral)
N2	Multiple regional lymph node metastases in true pelvis (perivesical, obturator, internal and external iliac, sacral)
N3	Lymph node metastases to the common iliac lymph nodes
Distant metastases	
M category	**Criteria**
M0	No distant metastases
M1	Distant metastases
M1a	Distant metastases limited to lymph nodes beyond the common iliac nodes
M1b	Non-lymph-node-distant metastases

Used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) *AJCC Cancer Staging Manual*, 8th Ed. Springer New York, 2017.

the pathologic stage (that based on removal of the bladder and regional lymph nodes). Over staging is relatively uncommon, but clinical under staging may occur in up to 53% of patients (Dutta et al, 2001; Skinner, 1982).

▶ Histopathology

Of all bladder cancers, 95% are epithelial malignancies, predominantly transitional cell carcinomas (TCCs). About 5% are adenocarcinomas, squamous cell carcinomas, neuroendocrine tumors, and other histologic subtypes.

A. Normal Urothelium

The normal urothelium is composed of three to seven layers of transitional cell epithelium resting on a basement membrane composed of extracellular matrix (collagen, adhesive glycoproteins, glycosaminoglycans) (Figure 19–2A). The epithelial cells vary in appearance; the basal cells are actively proliferating cells resting on the basement membrane; the luminal cells, perhaps the most important feature of normal bladder epithelium, are larger umbrella-like cells that are bound together by tight junctions. Beyond the basement membrane is loose connective tissue, the lamina propria, in which occasionally smooth-muscle fibers can be identified. These fibers should be distinguished from deeper, more extensive muscle elements defining the true muscularis propria.

B. Papilloma/PUNLMP

The World Health Organization (WHO) recognizes a papilloma as a papillary tumor with a fine fibrovascular stalk supporting an epithelial layer of transitional cells with normal thickness and cytology (Epstein et al, 1998). These are also termed **papillary urothelial neoplasms of low malignant potential** (PUNLMPs), which are a rare benign condition that do not require aggressive therapy.

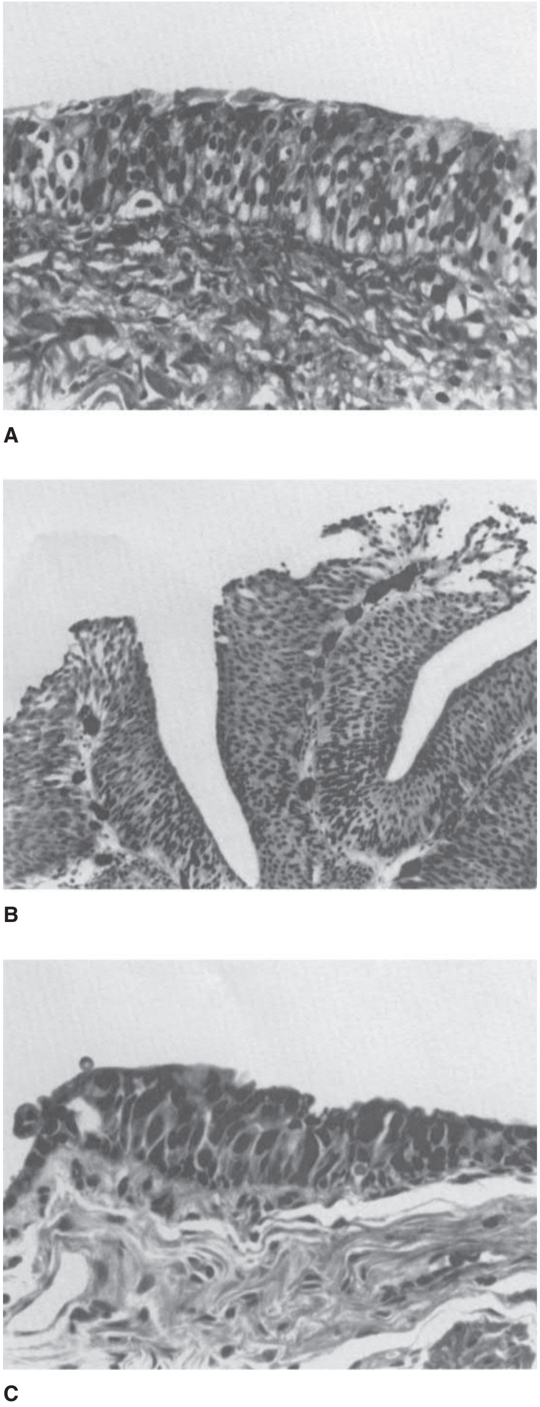
C. Urothelial (Transitional Cell) Carcinoma

Approximately 90% of all bladder cancers are TCCs. These are now more commonly referred to as **urothelial carcinomas**. These tumors most commonly appear as papillary, exophytic lesions (Figure 19–2B); less commonly, they may be sessile or ulcerated. Whereas the former group is usually superficial in nature, sessile growths are often invasive. Urothelial carcinomas can be composed purely of urothelial cells or have a minor component of a histologic variant. These variant histologies could be nested, microcystic, plasmatcytoid/signet ring, squamous, micropapillary, sarcomatoid, lymphoepithelioma-like, or lipid-rich; consist of clear cells or giant cells; be of Müllerian type; or have a poorly differentiated morphology. Tumors in a bladder diverticulum are also considered a divergent differentiation. These tumors are still regarded as urothelial carcinoma with "divergent differentiation" as per the WHO–International Society of Urologic Pathology (ISUP) classification (Humphrey et al, 2016).

Carcinoma in situ is recognizable as flat, anaplastic epithelium. The urothelium lacks the normal cellular polarity, and cells contain large, irregular hyperchromatic nuclei with prominent nucleoli (Figure 19–2C).

D. Nonurothelial Cell Carcinomas

1. Adenocarcinoma—Adenocarcinomas account for <2% of all bladder cancers. Primary adenocarcinomas of the bladder may be preceded by cystitis and metaplasia. Histologically, adenocarcinomas are mucus-secreting and may have glandular, colloid, or signet-ring patterns. Whereas



▲ **Figure 19–2.** ***A:*** Normal urothelium (125×). ***B:*** Moderately well differentiated, papillary bladder cancer (60×). ***C:*** Carcinoma in situ (200×).

primary adenocarcinomas often arise along the floor of the bladder, adenocarcinomas arising from the urachus occur at the dome. Both tumor types are often localized at the time of diagnosis, but muscle invasion is usually present.

2. Squamous cell carcinoma—Squamous cell carcinoma accounts for between 5% and 10% of all bladder cancers in the United States and is often associated here with a history of chronic infection, vesical calculi, or chronic catheter use. It may also be associated with bilharzial infection owing to *Schistosoma haematobium*, because squamous cell carcinoma accounts for approximately 60% of all bladder cancers in Egypt, parts of Africa, and the Middle East, where this infection is prevalent (El-Bolkainy et al, 1981). These tumors are often nodular and invasive at the time of diagnosis. Histologically they appear as poorly differentiated neoplasms composed of polygonal cells with characteristic intercellular bridges. Keratinizing epithelium is present, although often in small amounts.

3. Undifferentiated carcinomas—Undifferentiated bladder carcinomas, which are rare (accounting for <2%), have no mature epithelial elements. Very undifferentiated tumors with neuroendocrine features and small cell carcinomas tend to be aggressive and present with metastases (Choong et al, 2005; Quek et al, 2005).

E. Rare Epithelial and Nonepithelial Cancers

Rare epithelial carcinomas identified in the bladder include villous adenomas, carcinoid tumors, carcinosarcomas, and melanomas. Rare nonepithelial cancers of the urinary bladder include pheochromocytomas, lymphomas, choriocarcinomas, and various mesenchymal tumors (hemangioma, osteogenic sarcoma, and myosarcoma). Cancers of the prostate, cervix, and rectum may involve the bladder by direct extension. The most common tumors metastatic to the bladder include (in order of incidence) melanoma, lymphoma, stomach, breast, kidney, lung, and liver (Franks et al, 1999; Goldstein, 1967).

▶ Clinical Findings

A. Symptoms

Hematuria is the presenting symptom in 85–90% of patients with bladder cancer. It may be gross or microscopic, intermittent rather than constant. In a smaller percentage of patients, it is accompanied by symptoms of vesical irritability: frequency, urgency, and dysuria. Irritative voiding symptoms seem to be more common in patients with diffuse CIS. Symptoms of advanced disease include bone pain from bone metastases or flank pain from retroperitoneal metastases or ureteral obstruction. On occasion, locally extensive tumors can present with pain radiating to the buttocks and thighs.

B. Signs

Patients with large-volume or invasive tumors may be found to have bladder wall thickening or a palpable mass—findings that may be detected on a careful bimanual examination under anesthesia. If the bladder is not mobile, there may be fixation of tumor to adjacent structures by direct invasion.

Hepatomegaly and supraclavicular lymphadenopathy are signs of metastatic disease. Lower extremity lymphedema from occlusive pelvic lymphadenopathy may be seen occasionally. Patients may also present with back pain or pathologic fracture from bony metastases. On rare occasions, metastases can occur in unusual sites such as the skin presenting as painful nodules with ulceration (Block et al, 2006).

C. Laboratory Findings

1. Routine testing—The most common laboratory abnormality is hematuria. It may be accompanied by pyuria, which on occasion may result from concomitant urinary tract infection. Azotemia may be noted in patients with ureteral occlusion owing to the primary bladder tumor or lymphadenopathy. Anemia may be a presenting symptom owing to chronic blood loss, or replacement of the bone marrow with metastatic disease.

2. Urinary cytology—Cytologic examination of exfoliated cells found in voided urine or obtained by bladder irrigation may be especially useful in detecting bladder cancer. High-grade/stage tumors and as well as CIS are more likely to have a positive urine cytology unlike low-grade tumors.

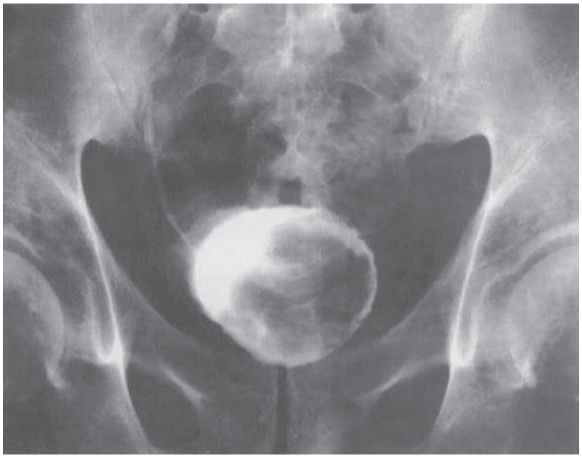
3. Other markers—Several new tests have been developed in order to overcome the shortcomings of urinary cytology such as the low sensitivity for low-grade superficial tumors and interobserver variability. Commercially available tests include the bladder tumor antigen (BTA) stat test, the BTA TRAK assay, the NMP22 assay, the NMP22 BladderChek test, the ImmunoCyt test, the UroVysion test, and the CxBladder test. These tests can detect cancer-specific proteins in urine (BTA/NMP22) or augment cytology by identifying cell surface or cytogenetic markers in the nucleus (UroVysion and ImmunoCyt). The CxBladder test detects specific mRNA in the urine and uses a mathematical model incorporating other patient-specific characteristics to predict the likelihood of cancer presence. Several other tests have been developed more recently (eg, AssureMdx, Xpert bladder cancer monitor) that are geared toward ruling out the presence of bladder cancer in patients undergoing hematuria evaluation. The most recent American Urologic Association guidelines for diagnosis and follow-up of asymptomatic microscopic hematuria in adults discourage the use of cytology or other urine markers in the evaluation of microscopic hematuria (Davis et al, 2012).

The AUA guidelines for management of non-muscle-invasitve bladder cancer do endorse use of the urinary markers for further evaluation of cases with "atypical" urine cytology and for assessment of response to intravesical therapy for bladder cancer (Chang et al, 2016).

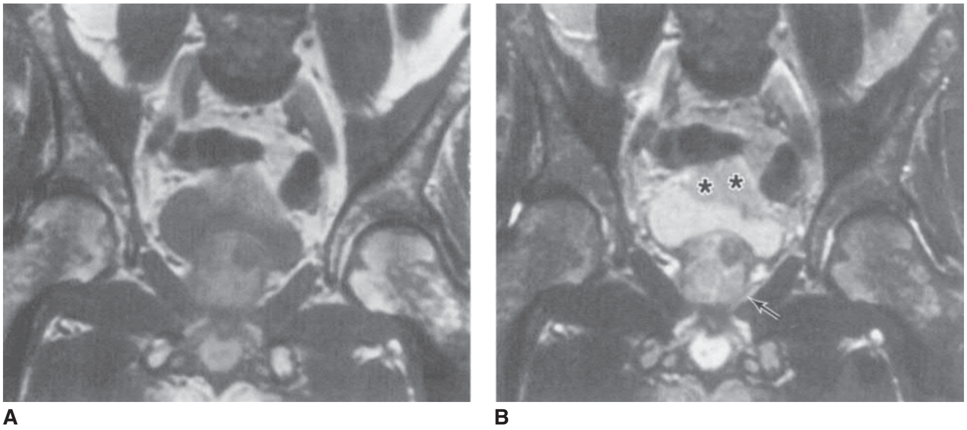
D. Imaging

Although bladder cancers may be detected by various imaging techniques, their presence is confirmed by cystoscopy and biopsy. Imaging is therefore used to evaluate the upper urinary tract and, when infiltrating bladder tumors are detected, to assess the depth of muscle wall infiltration and the presence of regional or distant metastases. Intravenous urography previously was one of the most common imaging tests for the evaluation of hematuria. However, it has virtually been replaced by computed tomography (CT) urography, which is more accurate, for evaluation of the entire abdominal cavity, renal parenchyma, and ureters in patients with hematuria (Gray Sears et al, 2002). Bladder tumors may be recognized as pedunculated, radiolucent filling defects projecting into the lumen (Figure 19–3); nonpapillary, infiltrating tumors may result in fixation or flattening of the bladder wall. Hydronephrosis from ureteral obstruction is usually associated with deeply infiltrating lesions and poor outcome after treatment (Haleblian et al, 1998).

Non-muscle-invasive (Ta, Tis, T1) bladder cancers staged with a properly performed TUR and examination under anesthesia do not require additional imaging of the bladder or pelvic organs. However, in the case of muscle-invasive tumors, both CT and magnetic resonance imaging (MRI) (Figure 19–4) have been used to characterize the extent of bladder wall invasion and detect enlarged pelvic lymph nodes, with overall staging accuracy ranging from 40% to 85% for CT. MRI appears to be particularly helpful



▲ **Figure 19–3.** Image of the urinary bladder obtained on an intravenous urogram. The filling defect represents a papillary bladder cancer.

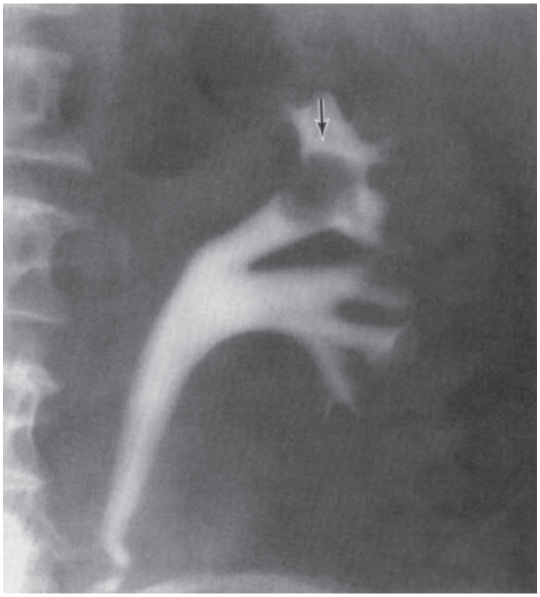


▲ **Figure 19–4.** MRI scan of invasive bladder carcinoma: ***(A)*** T1-weighted image; ***(B)*** T2-weighted image. Bladder wall invasion is best assessed on T2-weighted images because of heightened contrast between tumor (*asterisks*) and detrusor muscle along with ability to detect interruption of the thin high-intensity line representing normal bladder wall. The heterogeneous appearance of the prostate (*arrow*) on the T2-weighted image is due to benign prostatic hypertrophy, confirmed at cystectomy.

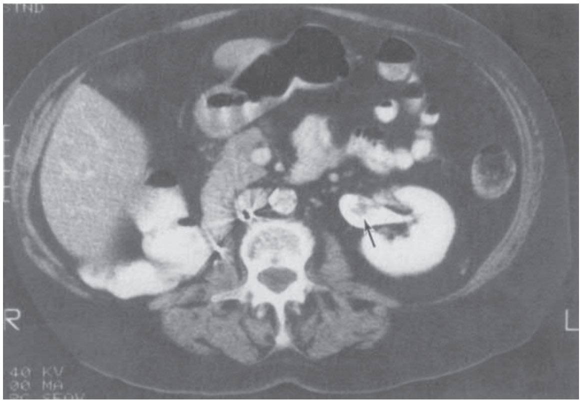
in assessing degree of local invasion to differentiate NMIBC from MIBC with a sensitivity of 91% and specificity of 89% (Woo et al, 2017). MRI performed using 3T scanners employing multiparameteric techniques appear to be most accurate. Both techniques rely on size criteria for the detection of lymphadenopathy; lymph nodes >1 cm are thought to be suggestive of metastases; unfortunately, small-volume pelvic lymph node metastases are often missed. Because invasive bladder cancers may metastasize to the lung or bones, staging of advanced lesions is completed with chest x-ray and radionuclide bone scan. Bone scans can be avoided if the serum alkaline phosphatase is normal (Berger et al, 1981). More recently, positron emission tomography (PET) CT scans have been utilized to assess metastases from bladder cancer (Figure 19–5). These data suggest that PET CT may detect microscopic nodal metastases or disease outside the pelvis and result in change in management in some cases (Kibel et al, 2009; Soubra et al, 2016).

E. Cystourethroscopy and Tumor Resection

The diagnosis and initial staging of bladder cancer is made by cystoscopy and transurethral resection (TUR). Cystoscopy can be performed with either flexible or rigid instruments, although the former is associated with less discomfort and requires only local anesthesia. Non-muscle-invasive, low-grade tumors usually appear as single or multiple papillary lesions. Higher-grade lesions are larger and sessile. CIS may appear as flat areas of erythema and mucosal irregularity. Use of fluorescent cystoscopy with blue light can enhance the ability to detect lesions by as much as 20% (Jocham et al, 2005). In this procedure, hematoporphyrin derivatives that accumulate preferentially in cancer cells are instilled into the bladder and fluorescence-incited using a blue light. Cancer cells with accumulated porphyrin such as 5-aminolevulinic acid or hexaminolevulinate (HAL) are detected as glowing red under the fluorescent light (Loidl et al, 2005). This



▲ **Figure 19–5.** Filling defect representing a transitional cell carcinoma (*arrow*) on retrograde pyelography.



▲ **Figure 19–6.** Computed tomography scan showing the presence of a renal pelvic tumor (*arrow*).

technology can be particularly useful in the detection of CIS (Figure 19–6). Narrowband imaging (NBI) is another technique that enhances detection of bladder tumors. It functions by using a filter that divides white light into two narrow bands of 415 and 540 nm. This allows for better differentiation of normal mucosal and submucosal vasculature from erythema due to CIS and hypervascular papillary bladder tumors. It can be performed using specific flexible cystoscopes by just switching the filter on without the need for any other maneuvers. However, randomized trial data suggest that this technique may not be as accurate as indicated by the initial studies (Naito et al, 2016).

Once a tumor is visualized or suspected, the patient is scheduled for examination under anesthesia and TUR or biopsy of the suspicious lesion. The objectives are tumor diagnosis, assessment of the degree of bladder wall invasion (staging), and complete excision of all visible lesions if possible. The American Urologic Associations' best practice guidelines for bladder cancer state that as a standard, all patients undergo as complete a resection as possible of all visible tumors (Chang et al, 2016).

Patients are placed in the lithotomy position. A careful bimanual examination is performed. The presence of any palpable mass and mobility of the bladder are noted along with any degree of fixation to contiguous structures. Cystoscopy is repeated with one or more lenses (30° and 70°) that permit complete visualization of the entire bladder surface. A resectoscope is then placed into the bladder, and visible tumors are removed by electrocautery. Suspicious areas may be biopsied with cup biopsy forceps, and the areas may be cauterized with an electrode. Some clinicians routinely perform random bladder biopsies of normal-appearing urothelium both close to and remote from the tumor. The value of random bladder biopsies is controversial. Detection of CIS on these biopsies can alter treatment, although studies suggest that only 1.5% of low-risk and 3.5% of high-risk patients may have tumor detected on such biopsies (van der Meijden et al, 1999; May et al, 2003). Findings of the random biopsy can alter treatment in up to 7% of patients (May et al, 2003). Using fluorescent cystoscopy may allow for more precise assessment of the completeness of tumor resection, thereby reducing the risk of leaving behind unresected tumor.

Natural History and Selection of Treatment

A. Standard Histopathological Assessment

The natural history of bladder cancers is defined by two separate but related processes: tumor recurrence and progression. Progression, including metastasis, represents the greater biologic risk. However, recurrence, even without progression, represents substantial patient morbidity in that it requires periodic reevaluation (cytology, cystoscopy, etc), repeat endoscopic ablation, and often intravesical chemotherapy (which may be costly, uncomfortable, and associated with complications). Treatment decisions are based on tumor stage and grade. Staging is performed using the tumor, node, metastasis (TNM) staging system (Figure 19–1), while grading has changed from the Ash–Broder system (I–III or I–IV). The WHO-ISUP system segregates tumors into urothelial dysplasia, urothelial papilloma, inverted papilloma, papilloma of uncertain malignant potential, papillary urothelial neoplasm of low malignant potential (PUNLMP), papillary urothelial carcinoma of low or high grade and urothelial carcinoma in situ (Humphrey et al, 2016).

At initial presentation, 74% of bladder tumors are non-muscle invasive—stage Tis, Ta, or T1 (David et al, 2009). Invasion into the muscle wall and beyond is identified in a smaller number of patients, and regional or distant metastases are found in approximately 25%. Unfortunately, most patients with invasive or metastatic disease have no previous history of bladder cancer. About 47% of the tumors are high grade and 53% are low grade at diagnosis (David et al, 2009). Most patients with T1 disease can be further subclassified into groups according to the level of lamina propria invasion. The depth of lamina propria invasion is predictive of the likelihood of recurrence and progression (Orsola et al, 2005). There are strong correlations between tumor grade and stage and tumor recurrence, progression, and survival (Frazier et al, 1993). Patients with low-stage, low-grade disease have a low risk (<5%) of progression to invasive disease, while as many as 40% of patients with low-stage but high-grade disease will progress with extended follow-up (Herr, 2000). Disease-free survival is excellent for patients with pathologically confirmed non-muscle-invasive disease (pT0, pT1, pTIS, 80–88%). However, it falls for patients with pT2 (53–80%), pT3 (39–68%), and pT4 (25–40%) tumors (Frazier et al, 1993; Stein et al, 2001; Trasher et al, 1994)—owing to the greater likelihood of metastasis in tumors of higher stage. Although lymph node metastases are uncommon (5%) in tumors of low stage, they are increasingly more common in higher stage tumors: 10–30% for pT3a, 31–46% for pT3b, and 35–64% for pT4 (Frazier et al, 1993; Stein et al, 2001). In patients with organ-confined disease, the presence of pelvic lymph node metastases appears to be the most important prognostic factor (Vieweg et al, 1999). The presence of lymphovascular invasion even in those with node-negative disease may portend a worse prognosis (Lotan et al, 2005).

Although metastasis is less common with superficial bladder cancers, such tumors may progress; most recur and require additional treatment. Tumor progression occurs in <6% of patients with Ta disease, but in up to 53% of those with T1 disease, with or without concomitant CIS (Cookson et al, 1997; Heney et al, 1983). Tumor progression occurs in 10–20% of patients with grade I tumors, 19–37% with grade II tumors, and 33–64% with grade III tumors (Lutzeyer et al, 1982; Torti et al, 1987). Using the more recent grading system, progression is observed in 5% of those with low-grade tumors, 15–40% with high-grade tumors, while PUNLMPs almost never demonstrate any risk of progression (Epstein et al, 1998).

Tumor recurrence is related to history of disease and grade, number, and size of the tumor. It is more common in the first 12–24 months after diagnosis (but can become manifest many years later), and patients with one recurrence are more likely to have another. Patients with T1, multiple (>4), large (>3), or high-grade tumors are at greater risk, as are those with either CIS or severe dysplasia in normal-appearing urothelium remote from the tumor site (Heney et al, 1983; Wolf et al, 1985). Tumors can be stratified into low-, intermediate- and high-risk categories on the basis of these criteria, and this stratification can be used to guide management decisions. Various nomograms and calculators have been developed that allow more individualized prediction of recurrence and progression in patients who receive intravesical chemo or immunotherapy (Sylvester et al, 2006; Fernandez-Gomez et al, 2009).

B. Treatment Selection

Management of non-muscle invasive bladder cancer (NMIBC) is based on risk stratification. The AUA and the European Association of Urology (EAU) have both described criteria for classification of tumors in low, intermediate and high-risk categories (Tables 20–2 and 20–3).

Patients with low-risk NMIBC that is characterized by a primary, single, papillary low-grade Ta tumor under 3 cm can be treated with TUR alone followed by a single instillation of intravesical chemotherapy immediately following TUR. Patients with intermediate-risk NMIBC can be treated with TUR followed by immediate postoperative intravesical chemotherapy instillation (single dose) and subsequent additional intravesical chemotherapy or immunotherapy with BCG. In some patients with recurrent, low-grade Ta tumors, fulguration of such tumors using electrocautery in an office setting under local anesthesia is also an acceptable alternative. Recent data suggest that some low-grade tumors can be observed at least for a while without significant increased risk of progression or metastases (Soloway et al, 2003). Patients with high-risk NMIBC should be managed with intravesical immunotherapy after complete and careful TUR. In patients with T1 tumors, a second resection of the same area may be required to accurately stage disease and determine treatment (Herr et al, 1999; Grimm et al, 2003). Repeat resections may also enhance response to intravesical therapy (Herr, 2005). More recent data suggest that repeat resections may not be necessary in patients with T1 tumors who had adequate muscle in the initial resection specimen as they are not likely to derive any benefit from repeat TUR (Gontero et al, 2016). According to the AUA guidelines, patients with T1 tumors can benefit from intravesical BCG therapy. Some patients with larger tumors, variant histology, or angiolymphatic invasion may be candidates for early radical cystectomy (Chang et al, 2016). Patients who recur after an initial trial with intravesical BCG therapy warrant more aggressive therapy such as cystectomy (Herr and Sogani, 2001).

Table 19–2. AUA risk stratification of NMIBC.

Low-risk	Intermediate-risk	High-risk
PUNLMP Single, low-grade Ta, ≤3 cm	Single, low-grade Ta >3 cm Low-grade Ta recurrent within 1 year Multifocal low-grade Ta Primary high-grade Ta ≤ 3cm Low-grade T1	Any CIS High-grade T1 High-grade Ta >3 cm (or multifocal) Any size recurrent high-grade Ta All high-grade Ta BCG failures Variant histology Lymphovascular invasion Prostatic urethral involvement with high-grade tumor

Adapted with permission from Chang SS, Boorjian SA, Chou R, et al: Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline, J Urol 2016 Oct;196(4):1021–1029.

Table 19–3. EAU guideline risk stratification for NMIBC.

Low-risk	Intermediate-risk	High-risk
Primary, single, low-grade Ta, ≤3 cm	Any not included in low-risk or high-risk category	Any CIS Any T1 Any HG tumor Multiple, recurrent, >3 cm low-grade Ta tumors

Adapted with permission from Babjuk M, Böhle A, Burger M, et al: EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016, Eur Urol 2017 Mar;71(3):447–461.

Patients with more invasive, but still localized, tumors (T2, T3) are candidates for more aggressive local treatment, including partial or radical cystectomy, or a combination of radiation and systemic chemotherapy. Radical TUR alone may be a viable option in select patients with T2 disease, particularly if no tumor is found on repeat resection since 10-year survival rates as high as 83% can be achieved (Herr, 2001). However, this approach must be used with caution since there is a substantial risk of leaving residual disease behind (Solsona et al, 1998). Patients with unresectable local tumors (T4b) are candidates for systemic chemotherapy, followed by surgery (or possibly irradiation) if they respond to the systemic therapy. Patients with either local or distant metastases should receive systemic chemotherapy followed by the selective use of either irradiation or surgery, depending on the response. More recently several new immunotherapy agents termed checkpoint inhibitors have been approved for the treatment of metastatic bladder cancer that appear to induce response in patients who have previously failed to respond to chemotherapy. However, response rates are still in the 20–30% range, and they can be accompanied by some unique side effects.

Treatment

A. Intravesical Chemotherapy

Immunotherapeutic or chemotherapeutic agents can be instilled into the bladder to reduce recurrence and/or progression, thereby avoiding the morbidity of systemic administration in most cases. Intravesical chemotherapy is used in two settings. When instilled immediately following TUR, it acts prophylactically to reduce tumor cell implantation (Solsona et al, 1999). It can also be used therapeutically to reduce risk of recurrence and progression particularly for low-risk NMIBC. Most agents are administered weekly for 6 weeks except when being used prophylactically where a single dose is administered immediately following TUR. Maintenance therapy may decrease recurrence rates further. Although local toxicity is relatively common (primarily irritative voiding symptoms), systemic toxicity is rare because of the limited absorption of drugs across the lumen of the bladder. Severe systemic complications can be avoided by not administering intravesical chemotherapy in patients with gross hematuria. Efficacy may be improved by increasing contact time and drug concentration (ie, by restricting fluid intake before administration, asking the patient to lie in different positions during treatment, avoiding instillation of air during drug administration, and requiring the patient to avoid urinating for 1–2 hours thereafter). The most common agents in the United States are mitomycin C and bacillus Calmette–Guérin (BCG). Patients in whom treatment with one agent fails may respond to another.

1. Mitomycin C—Mitomycin C is an antitumor, antibiotic, alkylating agent that inhibits DNA synthesis. With a molecular weight of 329, systemic absorption is minimal. The usual dose is 40 mg in 40 mL of sterile water or saline given once a week for 6 weeks. The same dose is utilized for a single prophylactic instillation. Between 39% and 78% of patients with residual tumor experience a complete response to intravesical mitomycin C (Kowalkowski and Lamm, 1988), and recurrence is reduced in 2–33% after complete TUR (Herr et al, 1987). Side effects are noted in 10–43% of patients and consist largely of irritative voiding symptoms, including urinary frequency, urgency, and dysuria. Unique to this drug is the appearance of a rash on the palms and genitalia in approximately 6% of patients, but this effect can be alleviated if patients wash their hands and genitalia at the time of voiding after intravesical administration. Instillation of mitomycin C into the bladder immediately post-TUR has been shown to decrease recurrences and prolong the interval to recurrence (Sylvester et al, 2004). Hence it is now considered standard of care to instill one dose of 40 mg of mitomycin C into the bladder immediately post-TUR to reduce the risk of recurrence (Chang et al, 2016). The efficacy of mitomycin C can be enhanced by administering it in a more concentrated solution of 40 mg in 20 nL of sterile water after alkalinizing the urine and with reduced fluid intake (Au et al, 2001).

2. Other intravesical chemotherapy agents—These include thiotepa, doxorubicin, epirubicin, and valrubicin. Thiotepa, doxorubicin, and epirubicin have been used in many studies and found to be effective, but mitomycin C is more commonly used as it is believed to be more effective compared to these other agents. Gemcitabine has also been used intravesically, particularly in patients who have not responded to BCG or other intravesical agents but also in the immediate postresection setting (Sternberg et al, 2013; Bohle et al, 2009). The side effect profiles of these agents are similar, and they are generally well tolerated. Gemcitabine also appears to cause less of an inflammatory reaction and is a cost-effective alternative to mitomycin.

3. BCG—BCG is an attenuated strain of *Mycobacterium bovis*. Many different strains of BCG exist, and the marketed preparations vary in the number, pathogenicity, viability, and immunogenicity of organisms (Catalona and Ratliff, 1990). The exact mechanism by which BCG exerts its antitumor effect is unknown, but it seems to be immunologically mediated. Mucosal ulceration and granuloma formation are commonly seen after intravesical instillation. Activated helper T lymphocytes can be identified in the granulomas, and interleukin-2 reportedly can be detected in the urine of treated patients (Haaf et al, 1986). BCG has been shown to be very effective both therapeutically and prophylactically. It appears to be the most efficacious intravesical agent for the management of CIS. Complete responses are recorded in 36–71% of patients with residual carcinoma (Catalona and Ratliff, 1990; Herr et al, 1987). Recurrence rates are reduced substantially in patients treated after endoscopic resection (11–27% vs a 70% recurrence after endoscopic resection alone)

(Catalona and Ratliff, 1990; Herr et al, 1985, 1987; Lamm, 1985). BCG has been shown to be superior to intravesical chemotherapy in preventing recurrence in patients with high-risk NMIBC (Lamm et al, 1991). Although BCG appears to be effective in delaying progression of high-risk superficial bladder cancer, 40–50% of these patients will experience disease progression with extended follow-up, and many patients will ultimately require cystectomy (Cookson et al, 1997; Davis et al, 2002; Herr et al, 1995). The most commonly recommended induction regimen for BCG is weekly for 6 weeks followed by a period of 6 weeks where no BCG is given. Maintenance therapy has shown proven benefit (Lamm et al, 2000; Oddens et al, 2013). The optimal regimen for maintenance therapy is unclear. Published regimens involve three instillations once a week at 3–6-month intervals for 3 years following TUR. Side effects are more commonly seen in patients receiving maintenance BCG therapy (van der Meijden et al, 2003; Lamm et al, 2000). Maintenance BCG appears to be more effective than intravesical chemotherapy with mitomycin C for intermediate- and high-risk superficial bladder cancer (Bohle et al, 2003). BCG is more effective than chemotherapy in preventing progression of non-muscle-invasive cancers (Sylvester et al, 2005). Most patients experience some degree of urinary frequency and urgency. Hemorrhagic cystitis occurs in approximately 7% of patients, and evidence of systemic BCG dissemination is found in <2%. Patients with mild systemic or moderate local symptoms should be treated with isoniazid (300 mg daily) and pyridoxine (vitamin B_6 50 mg/day), and the dosage of BCG should be reduced. Isoniazid is continued while symptoms persist and stopped 1 day before the next instillation. Routine prescription of quinolone antibiotics after BCG instillation has also been shown to reduce bladder related side effects.

Instillations should be discontinued in patients with severe systemic symptoms. Patients with prolonged high fever (>103°F), symptomatic granulomatous prostatitis, or evidence of systemic infection require treatment with isoniazid and rifampin (600 mg daily). Patients with signs and symptoms of BCG sepsis (eg, high fever, chills, confusion, hypotension, respiratory failure, jaundice) should be treated with isoniazid, rifampin, and ethambutol (1200 mg). The addition of cycloserine (500 mg twice daily) or prednisolone (40 mg daily) increases survival rates (Lamm, 1992).

4. New intravesical agents and approaches—Several investigators have studied the efficacy of single-dose therapy delivered at the time of complete TUR (Oosterlinck et al, 1993; Tolley et al, 1988). Such therapy has been shown to decrease recurrence rates, probably by decreasing the risk of tumor cell implantation at the time of initial cancer resection. Studies of interferon-α and valrubicin (an anthracycline derivative) suggest that these agents, either alone or perhaps in combination with other agents, may be effective in either high-risk patients or those who fail to respond to first-line therapy (Belldegrun et al, 1998; Sarosdy et al, 1998; Steinberg et al, 2000). Initial studies suggested that low-dose BCG in combination with interferon may be beneficial, but a subsequent randomized trial did not confirm the benefit of such an approach (O'Donnell et al, 2004, Nepple et al, 2010). Other agents that have been tested in the context of salvage intravesical therapy following BCG failure have been gemcitabine as well as docetaxel either individually or in combination. Gemcitabine showed promise in an early, phase I study, but subsequent studies have not demonstrated similar efficacy in this setting (Dalbagni et al, 2006). Phase II studies indicate that durable response can be achieved in about 30% of patients who have failed previous intravesical BCG (Skinner et al, 2013). Docetaxel also demonstrated a good response in an initial phase I study, but subsequent follow-up revealed that the response was not durable unless further induction and maintenance doses were administered (Barlow et al, 2009). Combination therapy with gemcitabine and mitomycin C as well as gemcitabine and docetaxel have been proven to yield responses in 30–40% of patients who have failed prior intravesical therapy with other agents (Breyer et al, 2010; Valaer et al, 2016).

B. Surgery

1. TUR—TUR is the initial form of treatment for all bladder cancers. It allows a reasonably accurate estimate of tumor stage and grade and the need for additional treatment. Patients with single, low-grade, noninvasive tumors may be treated with TUR alone; those with superficial disease but high-risk features should be treated with TUR followed by selective use of intravesical therapy, as described above. TUR alone has rarely been used in the management of patients with invasive bladder cancer because of a high likelihood of recurrence and progression. Such an approach has been used infrequently for carefully selected patients with comorbid medical conditions and either no residual disease or minimal disease only at restaging TUR of bladder tumor (Herr et al, 1987; Solsona et al, 1998). Careful follow-up of patients with superficial bladder cancers is mandatory because disease will recur in 30–80% of patients, depending on cancer grade, tumor stage, and number of tumors. Disease status at 3 months after initial resection is an important predictor of the risk of subsequent recurrence and progression (Holmang and Johansson, 2002; Solsona et al, 2000). Further surveillance is based on risk stratification of the patient into the low-, intermediate-, or high-risk groups. For patients with low-risk tumors who are free of recurrence at 3 months, repeat cystoscopy at 1 year is suggested. Patients who presented initially with intermediate- or high-risk tumors will require more frequent surveillance. In such patients, cystoscopy at 3-month intervals is necessary. Although periodic cystoscopy is suggested for all patients with a history of bladder cancer, the risk of recurrence decreases as the tumor-free interval increases. After 5 years without recurrence, the risk of recurrence has been estimated to be 22%; the rate is 2% for 10 years (Morris et al, 1995).

2. Partial cystectomy—Patients with solitary, infiltrating tumors (T1–T3) localized along the posterior lateral wall or dome of the bladder are candidates for partial cystectomy, as are patients with cancers in a diverticulum. Disease remote from the primary tumor must be excluded by random bladder biopsies preoperatively. Patients with concomitant CIS and those with lymph node metastases do not respond well to partial cystectomy (Holzbeierlein et al, 2004). Given current techniques of bladder replacement surgery, partial cystectomy is uncommonly indicated in the management of patients with invasive bladder cancer.

3. Radical cystectomy—Radical cystectomy implies removal of the anterior pelvic organs: in men, the bladder with its surrounding fat and peritoneal attachments, the prostate, and the seminal vesicles; in women, the bladder and surrounding fat and peritoneal attachments, cervix, uterus, anterior vaginal vault, urethra, and ovaries. This remains the gold standard of treatment for patients with muscle invasive bladder cancer. However, in select female patients, particularly in those who are premenopausal, the vaginal vault and urethra can be spared along with the uterus, fallopian tubes, and ovaries. Sparing of the urethra allows for construction of a neobladder that can be anastomosed to the urethral remnant. Disease-free survival 5 years after surgery is based on tumor stage: 88% for patients with PT0, PTa, or PTIS disease; 80% for patients with PT1 disease; 81% for patients with PT2 disease; 68% for patients with PT3a and 47% for those with PT3b disease; and 44% for patients with PT4a disease (Stein et al, 2001). Recurrences after surgery usually occur within the first 3 years. Local pelvic recurrence rates are low (7–10%); most patients who fail therapy have distant disease recurrence.

The risk of urethral tumor occurrence or recurrence in men who undergo radical cystectomy is 6.1–10.6%. Risk factors for urethral tumor involvement in men include infiltration of the prostatic stroma or prostatic urethra with cancer or CIS. Patients with these risk factors are candidates for urethrectomy either at the time of radical cystectomy or as a separate procedure (Zabbo and Montie, 1984). Although prostatic urethral disease is a risk factor for urethral recurrence, recent evidence suggests that urethrectomy may be omitted and orthotopic urinary diversion performed safely in men with only proximal prostatic urethral involvement and a negative urethral margin at radical cystectomy (Iselin et al, 1997).

Urethrectomy was once routinely performed in all women undergoing radical cystectomy. However, recent clinical experience suggests that bladder replacement is an acceptable procedure in women as well as men. Women with bladder cancer who have an uninvolved urethral margin at the time of cystectomy and whose tumor was not located at the bladder neck are candidates for this procedure. Approximately 66% of women undergoing radical cystectomy for the management of bladder cancer fall into this group (Stein et al, 1995, 1998; Stenzl et al, 1995).

In such women, even the uterus, substantial portion of the vaginal vault, fallopian tubes, and ovaries can be spared. A bilateral pelvic lymph node dissection is usually performed simultaneously with radical cystectomy. Lymph node metastases are identified in approximately 20–35% of patients (Stein et al, 2001)—an incidence that reflects the inability of any imaging mode to identify consistently small-volume lymph node metastases preoperatively. Patients with lymph node metastases have a poorer prognosis. However, some patients (10–33%) with limited disease in regional lymph nodes may be cured by radical cystectomy and lymphadenectomy (Stein et al, 2001;). Even patients with pathologically negative nodes appear to benefit from an extensive lymphadenectomy (Konety et al, 2003). Patients with fewer than five positive lymph nodes and organ-confined disease in the primary tumor tend to have a better prognosis than patients with more extensive disease. These patients may also benefit from adjuvant chemotherapy (see section on chemotherapy).

Urinary diversion may be accomplished using a variety of techniques. Methods have been developed that allow construction of reservoirs that are continent and do not require the patient to wear an external appliance for collection of urine (see Chapter 25).

C. Radiotherapy

External-beam irradiation (5000–7000 cGy), delivered in fractions over a 5–8-week period, is an alternative to radical cystectomy in well-selected patients with muscle-invasive bladder cancer. Treatment is generally well tolerated, but approximately 15% of patients may have significant bowel, bladder, or rectal complications. Five-year survival rates for stages T2 and T3 disease range from 18% to 41% (Quilty and Duncan, 1986). Unfortunately, local recurrence is common, occurring in approximately 33–68% of patients. Consequently, radiation as monotherapy is usually offered only to those patients who are poor surgical candidates due to advanced age or significant comorbid medical problems.

D. Chemotherapy

Approximately 15% of patients who present with bladder cancer are found to have regional or distant metastases; approximately 30–40% of patients with invasive disease develop distant metastases despite radical cystectomy or definitive radiotherapy. Without treatment, survival is limited. Early results with single chemotherapeutic agents and, subsequently, combinations of drugs have shown that a significant number of patients with metastatic bladder cancer respond partially or completely (Scher and Sternberg, 1985). The single most active agent is cisplatin, which, when used alone, produces responses in approximately 30% of patients (Yagoda, 1983). Other effective agents include methotrexate, doxorubicin, vinblastine, cyclophosphamide, gemcitabine, and 5-fluorouracil. Response rates improve when active agents are combined. The regimen of methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) has been the most commonly used for patients with advanced bladder cancer (Sternberg et al, 1988; Tannock et al, 1989). Approximately 13–35% of patients receiving such regimens attain a complete response. However, the median survival time is approximately 1 year, and the sustained survival rate is 20–25%. Treatment with MVAC is associated with substantial toxicity, including a toxic death rate of 3–4%.

Other newer agents demonstrating activity in this disease include ifosfamide, gemcitabine, paclitaxel, and gallium nitrate (Fagbemi and Stadler, 1998). A study demonstrated similar overall survival, time to treatment failure, and response rate for patients treated with MVAC and those treated with the combination of gemcitabine and cisplatin (von der Maase et al, 2000). The advantage of gemcitabine and cisplatin over MVAC is significantly lower toxicity and improved tolerability.

E. Immunotherapy

Although cytotoxic chemotherapy is the initial choice for those with advanced bladder cancer, such cancers have been shown to respond to immunotherapy, specifically programmed death ligand 1 (PD-L1), atezolizumab (Powles et al, 2014). Atezolizumab belongs to a class of agents termed checkpoint inhibitors (CTLA4, PD-1, PD-L1) that block ligands and receptors expressed by both tumor cells as well as immune cells in tumors (Massari et al, 2018). This class of agents helps rejuvenate the immune response to tumors by eliminating "checkpoints" that serve to suppress tumor-directed immune response. Cancers with a high mutational load may respond best. Atezolizumab has been approved for patients with metastatic urothelial cancer who have failed chemotherapy and is an option for those who are ineligible for cisplatin (Powles et al, 2018; Balar et al, 2017) therapy. Pembrolizumab is another PD-L1 inhibitor that has also been approved for treatment of metastatic bladder cancer (Plimack et al, 2017). Several other agents are also being investigated for use in the metastatic, adjuvant, and neoadjuvant setting.

F. Combination Therapy

Once it became apparent that patients with metastatic bladder cancer could benefit from combination chemotherapy, investigators began treating patients with locally invasive (T2–T4), but not metastatic, cancer similarly. Chemotherapy can be given before planned radical cystectomy (neoadjuvant) to decrease recurrence rates and, in selected cases, allow for bladder preservation. Approximately 22–43% of patients achieve a complete response to chemotherapy alone (Scher et al, 1988; Scher, 1990). However, additional treatment is still indicated because a substantial number of patients who were believed to be free of tumors after chemotherapy alone were found to have infiltrating disease at the time of surgery (Scher et al, 1989). Results from randomized trials suggest that neoadjuvant chemotherapy followed by surgery improves duration of survival when compared with surgery alone for patients with invasive disease (Grossman et al, 2003, International Collaboration of Trialists, Griffiths et al, 2011). Patients who undergo neoadjuvant chemotherapy are more likely to have no residual tumor in the bladder at cystectomy, and this portends a better long-term survival (Grossman et al, 2003). Patients who do not respond to neoadjuvant chemotherapy on the other hand, tend to derive no benefit or may even have worse survival (Zargar et al, 2015). Alternatively, adjuvant chemotherapy may be offered to selected patients after radical cystectomy because of an increased risk of recurrence due to the presence of locally advanced disease (ie, P3, P4, or N_+) (Freiha et al, 1996; Logothetis et al, 1988; Scher, 1990; Skinner et al, 1991; Stockle et al, 1992, 1995). These studies suggest that patients initially managed with radical cystectomy who are found to be at an increased risk of systemic relapse due to the presence of lymph node metastases or regionally advanced disease are candidates for adjuvant chemotherapy.

Owing to high local and systemic failure rates after definitive irradiation, several investigators have explored the possibility of combining irradiation with systemic chemotherapy to decrease recurrence rates, improve patient survival, and allow bladder preservation. Trials of single-agent chemotherapy and irradiation have shown better local response rates than are found in historical series of irradiation alone (Jakse et al, 1985; Pearson and Raghaven, 1985).

Muscle-invasive bladder cancer can also be managed with trimodality therapy that combines complete TUR followed by concomitant chemotherapy and radiation (Mak et al, 2014). Cisplatin and gemcitabine have been the chemotherapeutic agents with the best radio sensitizing activity in these regimens (Oh et al, 2009). Early cystectomy is offered to those who do not tolerate chemotherapy, radiation, or both owing to toxicity, and to those whose cancers fail to respond to such therapy. Complete response rates to chemo radiation may be as high as 50–70% initially, with 5-year overall survival rates approaching 50–82%. However, local recurrence is common, exceeding 50% in many of these studies. Studies with longer median follow-up of almost 7 years suggest that the occurrence of late failure with superficial disease recurrence may be around 26% (Zietman et al, 2001). However, patients who develop superficial disease recurrence (most commonly CIS) are more likely to require salvage cystectomy, as only 34% remain alive with a preserved bladder at 8 years compared to 61% of those who do not have such disease recurrence. Owing to invasive local recurrences, only 18–44% of patients may be alive with an intact bladder 5 years after chemo radiation. Local disease stage and completeness of initial TUR are predictive of response and survival, while delivery of radiation therapy by itself is not (Rodel et al, 2002). Predictors of poor outcome after combined chemo radiation for invasive bladder cancer include hydronephrosis at presentation, advanced clinical tumor stage, inability to complete the entire treatment protocol, and poor performance status.

A recent study has suggested that chemo radiation may also be inappropriate for patients with bladder tumors that are p53-positive (Herr et al, 1999). Combined chemotherapy and radiation has also been used successfully to treat high-grade superficially invasive tumors (T1) (Akcetin et al, 2005).

URETERAL AND RENAL PELVIC CANCERS

Incidence

Carcinomas of the renal pelvis and ureter are rare, accounting for only 4% of all urothelial cancers. The mean age at diagnosis is 65 years, and the male–female ratio is 2–4:1 (Babaian and Johnson, 1980). Urothelial cancer often presents as a widespread urothelial abnormality: Patients with a single upper tract carcinoma are at risk of developing bladder carcinomas (30–50%) and contralateral upper tract carcinoma (2–4%). Conversely, patients with primary bladder cancer are at low risk (<2%) of developing upper urinary tract cancers (Oldbring et al, 1989). However, patients with multiple, recurrent superficial and in situ bladder cancers that are successfully treated by TUR and BCG are at a substantial lifelong risk of development of upper tract cancers (Herr, 1998). The cumulative risks of such cancers have been estimated to be 10% at 5 years of follow-up, 26% at 5–10 years, and 34% at >10 years.

Etiology

As with bladder carcinoma, smoking and exposure to certain industrial dyes or solvents are associated with an increased risk of upper urinary tract TCCs. However, these tumors also occur with increased frequency in patients with a long history of excessive analgesic intake, those with Balkan nephropathy, and those exposed to Thorotrast, a contrast agent previously used for retrograde pyelography. Patients with carcinomas associated with analgesic abuse are more likely to be women, have higher stage disease, and be younger than others (Mahoney et al, 1977). All the major constituents of the analgesic compounds consumed (acetaminophen, aspirin, caffeine, and phenacetin) may be associated with an increased risk of upper urinary tract cancer (Jensen et al, 1989; Ross et al, 1989). Balkan nephropathy (which is similar to Chinese herb nephropathy) is an interstitial inflammatory disease of the kidneys that affects Yugoslavians, Rumanians, Bulgarians, and Greeks as well as Chinese (Miyazaki et al, 2017); associated upper tract carcinomas are generally superficial and more likely to be bilateral. The etiology is believed to be due to ingestion of the herb called **Aristolochia**, which releases aristocholic acid, which is a potent carcinogen. High levels of aristocholic acid cause mutations in the tumor suppressor gene p53, which can be responsible for the development of the tumors. Exposure to arsenic, which is found at high levels in well water used for drinking in some parts of the world, has also been associated with higher incidence of upper tract urothelial cancers. Patients with a condition called **Lynch syndrome**, which is observed in individuals with mutations of mismatch repair genes, are also prone to developing upper tract urothelial carcinomas (Crockett et al, 2011)

Pathology

The mucosal lining of the renal pelvis and ureter is similar to that of the urinary bladder, as it is composed of transitional cell epithelium. Thus, most renal pelvic and ureteral cancers (90% and 97%, respectively) are urothelial in origin. Grading is similar to the grading for bladder carcinomas. Papillomas account for approximately 15–20% of cases (Grabstald et al, 1971). They are isolated in just over 50% of patients and multiple in the rest, and in approximately 25% of patients with isolated papillomas and 50% of patients with multiple papillomas, carcinomas eventually develop. Among patients with carcinomas of the ureter, multicentricity approaches 50%. There is a relationship between tumor grade and the likelihood of urothelial abnormalities elsewhere. Low-grade cancers are associated with a low incidence of urothelial atypia or CIS in remote sites; however, these abnormalities are common with high-grade neoplasms (McCarron et al, 1982). Most upper urinary tract TCCs are localized at the time of diagnosis; the most common metastatic sites include regional lymph nodes, bone, and lung.

Squamous carcinomas account for approximately 10% of renal pelvic cancers and are much more rarely found in the ureter. Most carcinomas are sessile and infiltrating at the time of diagnosis. Such tumors are commonly identified in patients with a history of chronic inflammation from infection or calculus disease. Adenocarcinomas are very rare tumors of the upper urinary tract and, like squamous carcinomas, tend to be far advanced at the time of diagnosis.

Mesodermal tumors of the renal pelvis and ureter are quite rare. Benign tumors include fibroepithelial polyps (the most common), leiomyomas, and angiomas. Fibroepithelial polyps occur most commonly in young adults and are characterized radiographically by a long, slender, and polyploid filling defect within the collecting system. The most common malignant mesodermal tumors are leiomyosarcomas. The ureter and renal pelvis may be invaded by cancers of contiguous structures, such as primary renal, ovarian, or cervical carcinomas. True metastases to the ureter are rare. The most common metastatic tumors include those of stomach, prostate, kidney, and breast as well as lymphomas.

Staging and Natural History

Staging of both renal pelvic and ureteral carcinomas (Table 19–4) is based on an accurate assessment of the degree of tumor infiltration and parallels the staging system developed for bladder cancer (American Joint Committee on Cancer, 8th ed., 2018). Tumor stage and grade correlate with survival (Reitelman et al, 1987). Low-grade and low-stage cancers of the renal pelvis and ureter are associated with survival rates between 60% and 90%, compared with 0% and 33% for tumors of higher grade or those that have penetrated deep

Table 19–4. TNM staging of upper tract urothelial carcinoma.

T category	Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis
T3	For renal pelvis only; tumor invades beyond muscularis into peripelvic fat or into the renal parenchyma For ureter only; tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs or through the kidney into perinephric fat
Lymph nodes	
N category	**Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No lymph node metastases
N1	Metastases in a single lymph node ≤2 cm in greatest dimension
N2	Metastases in a single lymph node >2 cm, or multiple lymph nodes
Distant metastases	
M category	**Criteria**
M0	No distant metastases
M1	Distant metastases

Used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) *AJCC Cancer Staging Manual*, 8th Ed. Springer New York, 2017.

into or through the renal pelvic or ureteral wall (Hall et al, 1998). The latter figures reflect a high likelihood of regional or distant metastases—40% and 75% in patients with stages T2–T4 cancers, respectively. Upper urinary tract cancers are associated with a high rate of recurrent bladder cancer with as many as 40% of patients experiencing recurrent bladder tumors (Bagley and Grasso, 2010).

Clinical Findings

A. Symptoms and Signs

Gross hematuria is noted in 70–90% of patients. Flank pain, which is present in 8–50% of patients, is the result of ureteral obstruction from blood clots or tumor fragments, renal pelvic or ureteral obstruction by the tumor itself, or regional invasion by the tumor. Irritative voiding symptoms are present in approximately 5–10% of patients. Constitutional symptoms of anorexia, weight loss, and lethargy are uncommon and are usually associated with metastatic disease. A flank mass owing to hydronephrosis or a large tumor is detected in approximately 10–20% (Geerdsen, 1979), and flank tenderness may be elicited as well. Supraclavicular or inguinal adenopathy or hepatomegaly may be identified in a small percentage of patients with metastatic disease.

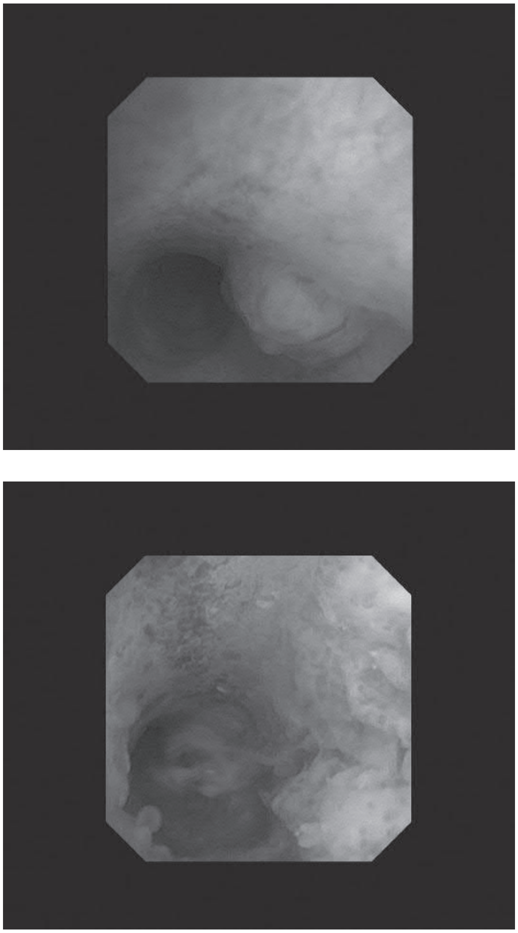
B. Laboratory Findings

Hematuria is identified in most patients but may be intermittent. Elevated liver function levels due to liver metastases are noted in a few patients. Pyuria and bacteriuria may be identified in patients with concomitant urinary tract infection from obstruction and urinary stasis.

As with bladder cancers, upper urinary tract cancers may be identified by examining exfoliated cells in the urinary sediment. In addition, specimens may be obtained directly with a ureteral catheter or by passing a small brush through the lumen of an open-ended catheter (Dodd et al, 1997; Gill et al, 1973). Detection depends on the grade of the tumor and the adequacy of the specimen obtained; 20–30% of low-grade cancers may be detected by cytologic testing compared with >60% of higher grade lesions (McCarron et al, 1983); using barbotage or a ureteral brush increases diagnostic accuracy. The utility of other markers, such as the UroVysion test, have been found to have better sensitivity and specificity relative to cytology of upper tract washings for the diagnosis of renal pelvis and ureteric tumors (Akkad et al, 2007).

C. Imaging

Findings on intravenous or CT urography in patients with upper urinary tract cancers are usually abnormal. The most common abnormalities identified include an intraluminal filling defect, unilateral nonvisualization of the collecting system, and hydronephrosis). Ureteral and renal pelvic tumors must be differentiated from nonopaque calculi, blood clots, papillary necrosis, and inflammatory lesions such as ureteritis cystica, fungus infections, or tuberculosis. The urography is often indeterminate, requiring retrograde pyelography for more accurate visualization of collecting-system abnormalities and simultaneous collection of cytologic specimens. CT urography is the test of choice for evaluating the upper tract. During retrograde pyelography, contrast material is injected into the ureteral orifice with a bulb or acorn-tip catheter. Intraluminal filling defects may then be identified in the ureter or renal pelvis (Figure 19–5). Ureteral tumors are often characterized by dilation of the ureter distal to the lesion, creating the appearance of a "goblet." Nonopaque ureteral calculi appear as a narrowing of the ureter distal to the calculus. A ureteral catheter passed up the ureter may coil distal to a ureteral tumor (Bergman's sign) (Bergman et al, 1961). Ultrasonography, CT, and MRI frequently identify soft-tissue abnormalities of the renal pelvis but may fail to identify ureteral filling defects directly, although they may show hydronephrosis (Figure 19–6). All three imaging techniques differentiate blood clot and tumor from nonopaque calculi. In addition, CT and MRI allow simultaneous examination



▲ **Figure 19–7.** Endoscopic appearance of high-grade sessile *(**A**)* and papillary *(**B**)* ureteric tumors.

of abdominal and retroperitoneal structures for signs of regional (lymph node) or more distant metastases.

D. Ureteropyeloscopy

The use of rigid and flexible ureteropyeloscopes has allowed direct visualization of upper urinary tract abnormalities (Figure 19–7). These instruments are passed transurethrally through the ureteral orifice; in addition, they (and the similarly constructed but larger nephroscopes) can be passed percutaneously into renal calyces and the pelvis directly. The latter instrument carries with it the theoretic possibility of tumor spillage along the percutaneous tract. Indications for ureteroscopy include evaluation of filling defects within the upper urinary tract and after positive results on cytologic study or after noting unilateral gross hematuria in the absence of a filling defect. Ureteroscopy is also performed as a surveillance procedure in patients who have undergone conservative surgery for removal of a ureteral or renal pelvic tumor. Visualization, biopsy, and, on occasion, complete tumor resection, fulguration, or laser vaporization of the tumor are possible endoscopically. Performance of ureteroscopy with biopsy to establish the diagnosis in a patient with positive urine cytology and an upper tract filling defect may not always be necessary as these patients are presumed to have upper tract TCC for which nephroureterectomy may be considered. However, any delay that may ensue from first performing an ureteroscopy with biopsy does not appear to jeopardize subsequent patient survival (Boorjian et al, 2005). Ureteroscopic visualization with biopsy is accurate and can identify cancer in most patients. A diagnosis of cancer can be obtained >90% of the time with grade determination possible in >80% of cases (Keeley et al, 1997). It is more difficult to obtain lamina propria or muscle in ureteroscopic cup biopsy specimens, which limits evaluation for stage of disease. Correlation of grade determined by tumor biopsy to that of the nephroureterectomy specimen is observed in 78% of cases. Biopsies tend to underestimate tumor grade in 22% of patients and stage in 45% of Ta tumors (Guarnizo et al, 2000). Multiple biopsies and biopsy of tumors in the proximal ureter tend to be more reliable in accurately determining stage and grade of ureteric tumors (Guarnizo et al, 2000).

▶ Treatment

Treatment of renal pelvic and ureteral tumors should be based primarily on grade, stage, position, and multiplicity. Renal function and anatomy should be assessed. The standard therapy for both tumor types has been nephroureterectomy with excision of a bladder cuff owing to the possibility of multifocal disease within the ipsilateral collecting system. This procedure may be performed using either an open or laparoscopic approach (Jarrett et al, 2001; Landman et al, 2002). When the operation is performed for proximal ureteral or renal pelvic cancers, the entire distal ureter with a small cuff of bladder needs to be removed to avoid recurrence within this segment (Reitelman et al, 1987; Strong et al, 1976). Tumors of the distal ureter may be treated with distal ureterectomy and ureteral reimplantation into the bladder if no proximal defects suggestive of cancer have been noted (Babaian and Johnson, 1980).

Indications for more conservative surgery, with endoscopic excision, tend to be limited to small, low-grade tumors that are solitary. In some cases, multiple low-grade tumors can be treated with resection and/or laser fulguration. Absolute indications for kidney-sparing procedures include tumor within the collecting system of a single kidney and bilateral urothelial tumors of the upper urinary tract or in patients with two kidneys but marginal renal function. In patients with two functioning kidneys, endoscopic excision alone should be considered only for low-grade and noninvasive tumors. One must realize that endoscopic examination may fail to detect the degree of infiltration adequately and therefore may understage some tumors. Current experience with endoscopic resection, fulguration, or vaporization suggests that the procedure is safe in properly selected patients (Blute et al, 1989). However, recurrences have been noted in 15–80% of patients treated with open or endoscopic excision (Blute et al, 1989; Keeley et al, 1997; Maier et al, 1990; Orihuela and Smith, 1988; Stoller et al, 1997). Recurrence may be avoided by treating with instillation of immunotherapeutic or chemotherapeutic agents such as BCG or mitomycin C (Keeley and Bagley, 1997; Orihuela and Smith, 1988; Studer et al, 1989). These agents can be delivered to the upper urinary tract through single or double-J ureteral catheters (Patel and Fuchs, 1998). If patients are treated conservatively, it has been suggested that routine follow-up should include routine endoscopic surveillance because imaging alone may be inadequate for detecting recurrence (Chen et al, 2000).

Radiotherapy plays a limited role in upper urinary tract cancers. Although controversial, postoperative irradiation is believed by some investigators to decrease recurrence rates and improve survival in patients with deeply infiltrating cancers. Patients with metastatic, transitional cell cancers of the upper urinary tract should receive cisplatin-based chemotherapeutic regimens as described for patients with metastatic bladder cancers. There is recent evidence suggesting that neoadjuvant chemotherapy in those with invasive upper tract tumors may be better tolerated and yield higher response rates as it is delivered in the setting of more normal renal function (Lane et al, 2010). Such therapy can also improve survival in patients with invasive upper tract cancers (Porten et al, 2014). Adjuvant chemotherapy does not appear to improve survival significantly in patients with upper urinary tract neoplasms (Necchi et al, 2018).

BIBLIOGRAPHY

Bladder Carcinomas

Akcetin Z et al: Radiochemotherapy after transurethral resection is an effective treatment method in T1G3 bladder cancer. Anticancer Res 2005;25:1623.

American Joint Committee on Cancer: Cancer Staging Manual. Lippincott, 1997.

Au J et al: Methods to improve efficacy of intravesical mitomycin C: Results of a randomized phase III trial. J Natl Cancer Inst 2001;93:597.

Babjuk M et al: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. Eur Urol 2013;64:639–653.

Balar AV et al: Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicentre, phase 2 trial. Lancet. 2017;389(10064):67–76.

Barlow L et al: A single-institution experience with induction and maintenance intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to bacille Calmette-Guérin therapy. BJU Int 2009;104:1098.

Belldegrun A et al: Superficial bladder cancer: The role of interferon-alpha. J Urol 1998;159:1793.

Berger GL et al: Lack of value of routine preoperative bone and liver scans in cystectomy candidates. J Urol 1981;125:637.

Block CE et al: Cutaneous metastases from transitional cell carcinoma of the bladder. Urology 2006;67:846.

Bohle A et al: Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90.

Bohle A et al: Single postoperative instillation of gemcitabine in patients with non-muscle invasive transitional cell carcinoma of the bladder: A randomised, double-blind, placebo controlled phase III multicentre study. Eur Urol 2009;56:495.

Breyer BN et al: Sequential intravesical gemcitabine and mitomycin C chemotherapy regimen in patients with non-muscle invasive bladder cancer. Urol Oncol 2010;28:510–514.

Cancer Genome Atlas Research Network: Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507:315–322.

Catalona WJ, Ratliff TL: Bacillus Calmette-Guérin and superficial bladder cancer. Surg Annu 1990;22:363.

Chang SS et al: Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol 2016; 196:1021–1029.

Choi W et al: Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 2014;25:152–165.

Choong NW et al: Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer 2005;103:1172.

Cookson MS, Sarosdy M: Management of stage T1 bladder cancer with intravesical bacillus Calmette-Guérin therapy. J Urol 1992;148:797.

Cookson MS et al: The treated natural history of high-risk superficial bladder cancer: 15-year outcome. J Urol 1997;158:62.

Dalbagni G et al: Genetic alterations in tp53 in recurrent urothelial cancer: A longitudinal study. Clin Cancer Res 2001;7:2797.

Dalbagni G et al: Phase II trial of intravesical gemcitabine in bacilli Calmette-Guérin refractory transitional cell carcinoma of the bladder. J Clin Oncol 2006;24:2729.

David KA et al: Surveillance of urothelial carcinoma: Stage and grade migration, 1993–2005 and survival trends, 1993–2000. Cancer 2009;115:1435.

Davis JW et al: Superficial bladder carcinoma treated with bacillus Calmette-Guerin: Progression-free and disease specific survival with minimum 10 year follow up. J Urol 2002;167:494.

Davis R et al: American Urological Association. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol 2012;188:2473–2481.

Dutta SC et al: Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. J Urol 2001;166:490.

El-Bolkainy MN et al: The impact of schistosomiasis on the pathology of bladder carcinoma. Cancer 1981;48:2643.

Elcock M, Morgan RW: Update on artificial sweeteners and bladder cancer. Regul Toxicol Pharmacol 1993;17:35.

Epstein JI et al: The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol 1998;22:1435.

Fagbemi S, Stadler W: New chemotherapy regimens for advanced bladder cancer. Semin Urol Oncol 1998;16:23.

Fairchild WV et al: The incidence of bladder cancer after cyclophosphamide therapy. J Urol 1979;122:163.

Fernandez-Gomez J et al: Predicting non-muscle invasive bladder cancer recurrence and progression in patients treated with Bacillus Calmette-Guerin: The CUETO scoring model. J Urol 2009;182: 2195–2203.

Franks ME et al: Hepatocellular carcinoma metastatic to the bladder after liver transplantation. J Urol 1999;162:799.

Frazier HA et al: The value of pathologic factors in predicting cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer 1993;71:3993.

Freiha F et al: A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine, and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996;155: 495.

Goldstein AG: Metastatic carcinoma to the bladder. J Urol 1967;98:209.

Gontero P et al: The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette-Guérin. BJU Int 2016;118:44–52.

Gray Sears CL et al: Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. J Urol 2002;168:2457.

Grimm MO et al: Effect of routine repeat transurethral resection for superficial bladder cancer: A long-term observational study. J Urol 2003;170:433.

Grossfeld GD et al: Evaluation of asymptomatic microscopic hematuria in adults (Part II): American Urological Association Best Practice Policy. Urology 2001;57:604.

Grossman HB et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. New Engl J Med 2003;349:859.

Haaf EO et al: Detection of interleukin 2 in urine of patients with superficial bladder tumors after treatment with intravesical BCG. J Urol 1986;136:970.

Haleblian GE et al: Hydronephrosis as a prognostic indicator in bladder cancer patients. J Urol 1998;160:2011.

Hall CG et al: Guideline for the management of nonmuscle invasive bladder cancer (stage Ta, T1, and Tis): 2007 update. J Urol 2007;178:2314.

Heney NM et al: Superficial bladder cancer: Progression and recurrence. J Urol 1983;130:1083.

Herr HW: Progression of stage T1 bladder tumors after intravesical bacillus Calmette-Guérin. J Urol 1991;145:40.

Herr HW: The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999;162:74.

Herr HW: Tumor progression and survival of patients with high grade, noninvasive papillary (TaG3) bladder tumors: 15-year outcome. J Urol 2000;163:60.

Herr HW: Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. J Clin Oncol 2001;19:89.

Herr HW: Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette-Guerin therapy. J Urol 2005;174:2134.

Herr HW, Sogani PC: Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol 2001;166:1296.

Herr HW et al: Experience with intravesical bacillus Calmette-Guérin therapy of superficial bladder tumors. Urology 1985;25:119.

Herr HW et al: An overview of intravesical therapy for superficial bladder tumors. J Urol 1987;138:1363.

Herr HW et al: Superficial bladder cancer treated with bacillus Calmette-Guérin: A multivariate analysis of factors affecting tumor progression. J Urol 1989;141:22.

Herr HW et al: Intravesical bacillus Calmette-Guerin therapy prevents tumor progression and death from superficial bladder cancer: Ten-year follow-up of a prospective randomized trial. J Clin Oncol 1995;13:1404.

Herr HW et al: Can p53 help select patients with invasive bladder cancer for bladder preservation? J Urol 1999;161:20.

Hicks RM: Promotion in bladder cancer. Carcinogenesis 1982;7:139.

Holmang S, Johansson SL: Stage Ta–T1 bladder cancer: The relationship between findings at first follow up cystoscopy and subsequent recurrence and progression. J Urol 2002;167:1634.

Holzbeierlein J et al: Partial cystectomy: A contemporary review of the Memorial Sloan-Kettering Cancer Center experience and recommendations for patient selection. J Urol 2004;172:878.

Humphrey PA et al: The 2016 WHO classification of tumors of the urinary system and male genital organs: Part B: Prostate and bladder tumors. Eur Urol 2016;70:106–119.

International Collaboration of Trialists, Griffiths G et al: International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. J Clin Oncol 2011; 29:2171–2177.

Iselin C et al: Does prostate transitional cell carcinoma preclude orthotopic bladder reconstruction after radical cystoprostatectomy for bladder cancer? J Urol 1997;158:2123.

Jakse G et al: Combination of chemotherapy and irradiation for non-resectable bladder carcinoma. World J Urol 1985;3:121.

Jebar AH et al: FGFR3 and Ras gene mutations are mutually exclusive genetic events in urothelial cell carcinoma. Oncogene 2005;24:5218.

Jocham D et al: Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: A prospective, phase III multicenter study. J Urol 2005;174:862.

Kibel AS et al: Prospective study of [18F] fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol 2009;27:4314.

Knowles MA: Role of FGFR3 in urothelial carcinoma: Biomarker and potential therapeutic target. World J Urol 2007;25:581.

Konety BR, Getzenberg RH: Urine based markers of urological malignancy. J Urol 2001;165:600.

Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. J Urol. 2003 Mar;169(3):946–50.

Kowalkowski TS, Lamm DL: Intravesical chemotherapy of superficial bladder cancer. In: Resnick M (ed): Current Trends in Urology. Williams & Wilkins, Philadelphia, 1988.

Lamm DL: Bacillus Calmette-Guérin immunotherapy for bladder cancer. J Urol 1985;134:40.

Lamm DL: Complications of bacillus Calmette-Guérin immunotherapy. Urol Clin North Am 1992;19:565.

Lamm DL et al: A randomized trial of intravesical doxorubicin and immunotherapy with bacillus Calmette-Guérin for transitional cell carcinoma of the bladder. New Engl J Med 1991;325:1205.

Lamm DL et al: Maintenance bacillus Calmette-Guérin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group study. J Urol 2000;163:1124.

Logothetis CJ et al: Adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy for bladder cancer: An update. J Clin Oncol 1988;6:1590.

Loidl W et al: Flexible cystoscopy assisted by hexaminolevulinate induced fluorescence: A new approach for bladder cancer detection and surveillance? Eur Urol 2005;47:323.

Lotan Y et al: Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. J Clin Oncol 2005;23:6533.

Lotan Y et al: Modeling cost-effectiveness of a biomarker-based approach to neoadjuvant chemotherapy for muscle-invasive bladder cancer. BJU Int 2018;31 (doi: 10.1111/bju.14220. [Epub ahead of print] PubMed). [PMID: 29603871]

Lutzeyer W et al: Prognostic parameters in superficial bladder cancer: An analysis of 315 cases. J Urol 1982;127:250.

Mak RH et al: Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol 2014;32:3801–3809.

Massari F et al: Immune checkpoint inhibitors for metastatic bladder cancer. Cancer Treat Rev 2018;64:11–20.

Matanoski GM, Elliott EA: Bladder cancer epidemiology. Epidemiol Rev 1981;3:203.

May F et al: Significance of random bladder biopsies in superficial bladder cancer. Eur Urol 2003;44:47.

Miyao N et al: Role of chromosome 9 in human bladder cancer. Cancer Res 1993;53:4066.

Morris S et al: Superficial bladder cancer: How long should a tumor-free patient have check cystoscopies? Br J Urol 1995;75:193.

Naito S et al: CROES Narrow Band Imaging Global Study Group. The Clinical Research Office of the Endourological Society (CROES) Multicentre Randomised Trial of Narrow Band Imaging-Assisted Transurethral Resection of Bladder Tumour (TURBT) Versus Conventional White Light Imaging-Assisted TURBT in Primary Non-Muscle-invasive Bladder Cancer Patients: Trial Protocol and 1-year results. Eur Urol 2016;70:506–515.

Nepple KG et al: Bacillus Calmette-Guérin with or without interferon α-2b and megadose versus recommended daily allowance vitamins during induction and maintenance intravesical treatment of nonmuscle invasive bladder cancer. J Urol 2010;184:1915–1919.

O'Donnell MA et al: Interim results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alfa-2b for superficial bladder cancer. J Urol 2004;172:888.

Oddens J et al: Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: One-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462–472.

Oh KS et al: Combined-modality therapy with gemcitabine and radiation therapy as a bladder preservation strategy: Long-term results of a phase I trial. Int J Radiat Oncol Biol Phys 2009;74:511.

Olumi AF et al: Molecular analysis of human bladder cancer. Semin Urol 1990;8:270.

Oosterlinck W et al: A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. J Urol 1993;149:749.

Orsola A et al: Initial high-grade T1 urothelial cell carcinoma: Feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. Eur Urol 2005;48:231.

Pearson BS, Raghaven D: First line intravenous cisplatin for deeply invasive bladder cancer: Update on 70 cases. Br J Urol 1985;57:690.

Plimack ER et al: Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): A non-randomised, open-label, phase 1b study. Lancet Oncol 2017;18:212–220.

Ploussard G et al: Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: A systematic review. Eur Urol 2014;66:120–137.

Powles T et al: MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528): 558–562.

Powles T et al: Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391(10122):748–757.

Quek ML et al: Radica cystectomy for primary neuroendocrine tumors of the bladder: The University of Southern California experience. J Urol 2005;174:93.

Quilty PM, Duncan W: Primary radical radiotherapy for T3 transitional cell cancer of the bladder: Analysis of survival and control. Int J Radiat Oncol Biol Phys 1986;12:853.

Robertson AG et al: Comprehensive molecular characterization of muscle invasive bladder cancer. Cancer Cell 2017;71:540–556.

Rodel C et al: Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. J Clin Oncol 2002;20:3061.

Saint-Jacques N et al: Arsenic in drinking water and urinary tract cancers: A systematic review of 30 years of epidemiological evidence. Environ Health 2014;13:44.

Sarosdy M et al: Oral bropirimine immunotherapy of bladder carcinoma in situ after prior intravesical bacille Calmette-Guérin. Urology 1998;51:226.

Scher HI: Neoadjuvant therapy of invasive bladder tumors. In: Williams R, Carroll PR (eds): Treatment Perspectives in Urologic Oncology. Pergamon Press, New York, 1990.

Scher HI, Sternberg CN: Chemotherapy of urologic malignancies. Semin Urol 1985;3:239.

Scher HI et al: Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 1988;139:470.

Scher HI et al: Neoadjuvant chemotherapy for invasive bladder cancer: Experience with the M-VAC regimen. Br J Urol 1989;64:250.

Seiler R et al: Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol 2017;72:544–554.

Serretta V et al: Urinary NMP22 for the detection of recurrence after transurethral resection of transitional cell carcinoma of the bladder: Experience in 137 patients. Urology 1998;52:793.

Sidransky D et al: Identification of p53 gene mutations in bladder cancers and urine samples. Science 1991;252:706.

Silverman DT et al: Bladder cancer. In: Schottenfeld D, Fraumeni JF Jr (eds): Cancer Epidemiology and Prevention. Oxford University Press, New York, 2006, pp. 1101–1127.

Skinner DG: Management of invasive bladder cancer: A meticulous lymph node dissection can make a difference. J Urol 1982;128:34.

Skinner DG et al: The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: A prospective comparative trial. J Urol 1991;145:459.

Skinner EG et al: SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guérin. J Urol 2013;190:1200–1204.

Soloway MS et al: Expectant management of small, recurrent, noninvasive papillary bladder tumors. J Urol 2003;170:438.

Solsona E et al: Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: Long-term follow up of a prospective study. J Urol 1998;159:95.

Solsona E et al: Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: Short and long-term follow up. J Urol 1999;161:1120.

Solsona E et al: The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 2000;164:685.

Soubra A et al: The diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography and computed tomography in staging bladder cancer: a single-institution study and a systematic review with meta-analysis. World J Urol 2016;34:1229–1237.

Stein JP et al: Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: A pathological review of female cystectomy specimens. J Urol 1995;154:1329.

Stein JP et al: Prospective pathologic analysis of female cystectomy specimens: Risk factors for orthotopic diversion in women. Urology 1998;51:951.

Stein JP et al: Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol 2001;19:666.

Steinberg G et al: Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guérin refractory carcinoma in situ of the bladder. J Urol 2000;163:761.

Stenzl A et al: The risk of urethral tumors in female bladder cancer: Can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol 1995;153(3 Pt 2):950.

Sternberg CN et al: M-VAC (methotrexate vinblastine doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 1988;139:461.

Sternberg IA et al: Intravesical gemcitabine for high risk, nonmuscle invasive bladder cancer after bacillus Calmette-Guérin treatment failure. J Urol 2013;190:1686.

Stockle M et al: Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: Long-term results of a controlled prospective study and further clinical experience. J Urol 1995;153:47.

Stockle M et al: Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): Improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective trial. J Urol 1992;148:302.

Sylvester RJ et al: A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: A meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186.

Sylvester RJ et al: Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: A meta-analysis of the published results of randomized clinical trials. J Urol 2005;174:86.

Sylvester RJ et al: Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using eortc risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–477.

Tannock I et al: M-VAC (methotrexate vinblastine doxorubicin and cisplatin) chemotherapy for transitional cell carcinoma: The Princess Margaret Hospital experience. J Urol 1989;142:289.

Tolley D et al: Effect of mitomycin C on recurrence of newly diagnosed superficial bladder cancer: Interim report from the Medical Research Council Subgroup on Superficial Bladder Cancer. Br Med J 1988;296:1759.

Torti FM et al: Superficial bladder cancer: The primacy of grade in the development of invasive disease. J Clin Oncol 1987;5:125.

Trasher JB et al: Clinical variables which serve as predictors of cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer 1994;73:1708.

Tsai YC et al: Allelic losses of chromosomes 9, 11, and 17 in human bladder cancer. Cancer Res 1990;50:44.

Valaer KN et al: Experience with sequential intravesical gemcitabine and docetaxel as salvage therapy for non-muscle invasive bladder cancer. Curr Urol Rep 2016;17:38.

van der Meijden A et al: Significance of bladder biopsies in Ta, T1 bladder tumors: A report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. Eur Urol 1999;35:267.

van der Meijden A et al: Maintenance bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: Results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. Eur Urol 2003;44:429.

Vieweg J et al: Impact of primary stage on survival in patients with lymph node positive bladder cancer. J Urol 1999;161:72.

von der Maase H et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter phase III study. J Clin Oncol 2000;17:3068.

Wolf H et al: Urothelial dysplasia concomitant with bladder tumours: A determinant for future new occurrences in patients treated by full course radiotherapy. Lancet 1985;I:1005.

Woo S et al: Diagnostic performance of MRI for prediction of muscle invasiveness of bladder cancer: A systematic review and meta analysis. Eur J Radiol 2017;95:46.

Yagoda A: Chemotherapy for advanced urothelial cancer. Semin Urol 1983;1:60.

Zabbo A, Montie JE: Management of the urethra in men undergoing radical cystectomy for bladder cancer. J Urol 1984;131:267.

Zargar H et al: Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol 2015; 67:241–249.

Zietman AL et al: Selective bladder conservation using transurethral re-section, chemotherapy, and radiation: Management and consequences of Ta, T1, and Tis recurrence within the retained bladder. Urology 2001;58:380.

Ureteral and Renal Pelvic Cancers

Akkad T et al: Fluorescence in situ hybridization for detecting upper urinary tract tumors–a preliminary report. Urology 2007; 70:753.

American Joint Committee on Cancer: Cancer Staging Manual. Lippincott-Raven, Philadelphia, 1997.

Babaian RJ, Johnson DE: Primary carcinoma of the ureter. J Urol 1980;123:357.

Bagley DH, Grasso M: Uretersocopic laser treatment of upper urinary tract neoplasms. World J Urol 2010;28:143.

Bergman H et al: New roentgenologic signs of carcinoma of the ureter. Am J Roentgenol 1961;86:707?

Blute ML et al: Impact of endourology on diagnosis and management of upper urinary tract urothelial cancer. J Urol 1989;141:1298.

Boorjian S et al: Impact of delay to nephroureterectomy for patients undergoing ureteroscopic biopsy and laser tumor ablation of upper tract transitional cell carcinoma. Urology 2005;66:283.

Chen GL et al: Surveillance of upper tract transitional cell carcinoma: The role of ureteroscopy, retrograde pyelography, cytology and urinalysis. J Urol 2000;164:1901.

Crockett DG et al: Upper urinary tract carcinoma in Lynch syndrome cases. J Urol 2011;185:1627.

Dodd L et al: Endoscopic brush cytology of the upper urinary tract: Evaluation of its efficacy and potential limitations in diagnosis. Acta Cytol 1997;41:377.

Geerdsen J: Tumours of the renal pelvis and ureter: Symptomatology, diagnosis, treatment, and prognosis. Scand J Urol Nephrol 1979;13:287.

Gill WB et al: Retrograde brushing: A new technique for obtaining histologic and cytologic material from ureteral renal pelvic and renal caliceal lesions. J Urol 1973;109:573.

Grabstald H et al: Renal pelvic tumors. JAMA 1971;218:845.

Guarnizo E et al: Ureteroscopic biopsy of upper tract urothelial carcinoma improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. J Urol 2000;163:52.

Hall M et al: Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: A 30-year experience in 252 patients. Urology 1998;52:594.

Herr H: Long-term results of BCG therapy: Concern about upper tract tumors. Semin Urol Oncol 1998;16:13.

Jarrett TW et al: Laparoscopic nephroureterectomy for the treatment of transitional cell carcinoma of the upper urinary tract. Urology 2001;57:448.

Jensen OM et al: The Copenhagen case-control study of renal pelvis and ureter cancer: Role of analgesics. Int J Cancer 1989;44:965.

Keeley F et al: Ureteroscopic treatment and surveillance of upper urinary tract transitional cell carcinoma. J Urol 1997;157:1560.

Keeley FX, Bagley DH: Adjuvant mitomycin C following endoscopic treatment of upper tract transitional cell carcinoma. J Urol 1997;158:2074.

Keeley FX et al: Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. J Urol 1997;157:33.

Landman J et al: Comparison of hand assisted and standard laparoscopic radical nephroureterectomy for the management of localized transitional cell carcinoma. J Urol 2002;167:2387.

Lane BR et al: Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. Cancer 2010;116:2967.

Mahoney JF et al: Analgesic abuse renal parenchymal disease and carcinoma of the kidney or ureter. Austral N Z J Med 1977;7:463.

Maier U et al: Organ-preserving surgery in patients with urothelial tumors of the upper urinary tract. Eur Urol 1990;18:197.

McCarron JP et al: Systematic mapping of nephrouretectomy specimens removed for urothelial cancer: Pathological findings and clinical correlations. J Urol 1982;128:243.

McCarron JP et al: Tumors of the renal pelvis and ureter: Current concepts and management. Semin Urol 1983;1:75.

Miyazaki J et al: Epidemiology of urothelial carcinoma. Int J Urol 2017;24:730–734.

Necchi A et al: Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: A joint study by the European Association of Urology-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration. BJU Int 2018;121:252–259.

Oldbring J et al: Carcinoma of the renal pelvis and ureter following bladder carcinoma: Frequency risk factors and clinicopathological findings. J Urol 1989;141:1311.

Orihuela E, Smith AD: Percutaneous treatment of transitional cell carcinoma of the upper urinary tract. Urol Clin North Am 1988;15:425.

Patel A, Fuchs G: New techniques for the administration of topical adjuvant therapy after endoscopic ablation of upper urinary tract transitional cell carcinoma. J Urol 1998;159:71.

Porten S et al: Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. Cancer 2014;120:1794–1799.

Reitelman C et al: Prognostic variables in patients with transitional cell carcinoma of the renal pelvis and proximal ureter. J Urol 1987;138:1144.

Ross RK et al: Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter. Cancer Res 1989;49:1045.

Stoller M et al: Endoscopic management of upper tract urothelial tumors. Tech Urol 1997;3:152.

Strong DW et al: The ureteral stump after nephroureterectomy. J Urol 1976;115:654.

Studer UE et al: Percutaneous bacillus Calmette-Guérin perfusion of the upper urinary tract for carcinoma in situ. J Urol 1989;142: 975.

Zimmerman R et al: Utility of the Bard BTA test in detecting upper urinary tract transitional cell carcinoma. Urology 1998;51:956.

Renal Parenchymal Neoplasms

20

Anobel Y. Odisho, MD, MPH; & Kirsten L. Greene, MD, MS

RENAL MASSES

Epidemiology

In the United States in 2018, there were an estimated 65,340 new cases of upper tract renal masses leading to 14,970 estimated deaths, representing 2–3% of all cancer cases (Siegel et al, 2018). The incidence is twice as high in men as women. While the incidence of renal cell carcinoma is increasing worldwide, with the highest rates in more developed countries, the age-standardized mortality rates appear to be stabilizing overall and in fact decreasing in western/northern Europe, the United States, and Australia (Znaor et al, 2015). The overall increase in incidence is driven primarily by the increasing availability and use of imaging.

Clinical Presentation

A. Signs and Symptoms

The classically described triad of gross hematuria, flank pain, and a palpable mass occurs in only 7–10% of patients and is frequently a manifestation of advanced disease. Gross or microscopic hematuria can be seen in up to 60% of patients presenting with renal cell carcinoma (RCC). Patients presenting with hematuria should also be evaluated with cystoscopy to rule out urothelial carcinoma. Patients may also present with dyspnea, cough, and bone pain that are typically symptoms secondary to metastases. However, with increasing use of imaging, approximately 60–70% of renal tumors are detected incidentally (Herts et al, 2018; Novara et al, 2010).

B. Paraneoplastic Syndromes

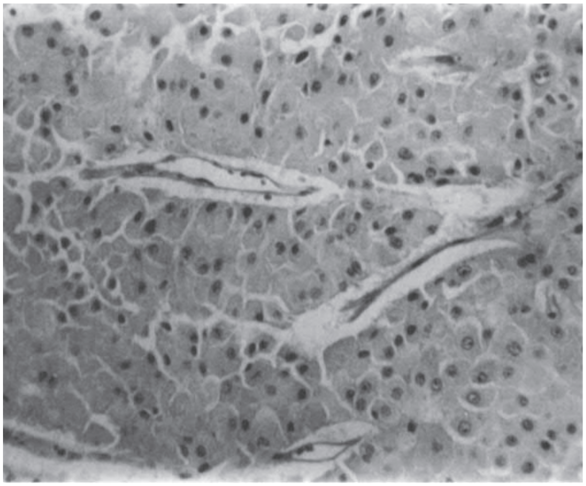
Renal cell carcinoma is associated with a wide spectrum of paraneoplastic syndromes, including polycythemia, thrombocytosis, hypercalcemia, cachexia, pyrexia, hypertension, and hepatic dysfunction, which may be driven by VEGF expression (Ding et al, 2013). While these manifestations are reported in 10–40% of patients with RCC, this may be overestimated because of publication bias (Hegemann et al, 2018). Paraneoplastic symptoms are not associated with increasing disease stage and should be regarded as a diagnosis of exclusion (Kim et al, 2003).

Hypercalcemia is the most common paraneoplastic complication in renal cell carcinoma, and has been reported to occur in up to 13% of patients with RCC (Kim et al, 2003). Hypercalcemia may be due to production of a parathyroid hormone-related peptide (PTHrP) that mimics the function of parathyroid hormone (Papworth et al, 2005; Goldner, 2016). RCC is the most common cause of paraneoplastic erythrocytosis, which is reported to occur in 3–10% of patients with this tumor (Sufrin et al, 1989). In 1961, Stauffer described a reversible syndrome of hepatic dysfunction in the absence of hepatic metastases associated with RCC (Stauffer, 1961). Hepatic function abnormalities include elevation of alkaline phosphatase and bilirubin, hypoalbuminemia, prolonged prothrombin time, and hypergammaglobulinemia. Stauffer's syndrome tends to occur in association with fever, fatigue, and weight loss and typically resolves after tumor resection. The reported incidence of Stauffer's syndrome varies from 3% to 20% (Gold et al, 1996).

C. Laboratory Findings

In addition to the laboratory abnormalities associated with the various RCC paraneoplastic syndromes, anemia, microscopic hematuria, and an elevated sedimentation rate are frequently observed. Anemia occurs in about 30% of RCC patients. The anemia typically is not secondary to blood loss or hemolysis and is commonly normochromic. The serum iron and total iron-binding capacity are usually low, as in the anemia of chronic disease. Iron therapy is usually ineffective; however, surgical removal of tumors usually leads to physiologic correction of the anemia.

The incidence of an elevated erythrocyte sedimentation rate has been reported to be as high 75%. CRP is often

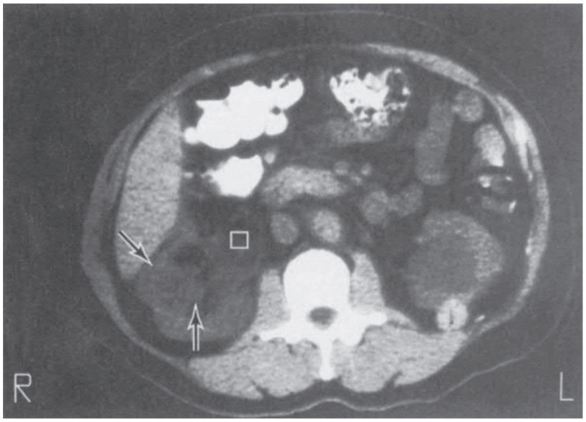


▲ **Figure 20–1.** Histologic section of a grade I (benign renal oncocytoma (original magnification, ×100).

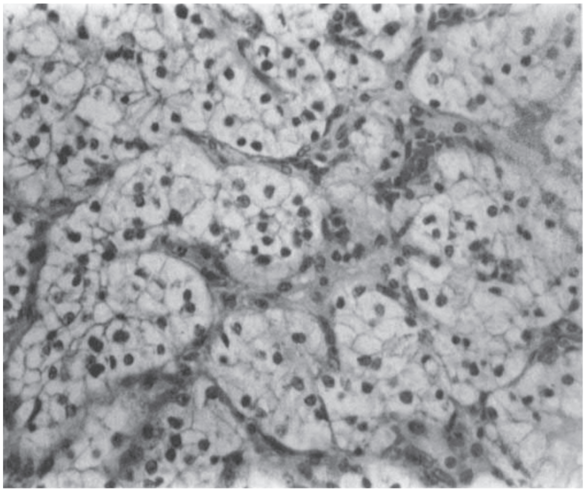
elevated with RCC and can be prognostic of recurrence (Karakiewicz et al, 2007; Steffens et al, 2012). These findings are nonspecific, and normal findings do not rule out a diagnosis of RCC. Urine cytology is not useful in the diagnosis of RCC, but it can be used to rule out urothelial carcinoma during initial evaluation, specifically in patients with hematuria.

Radiographic Findings

Although radiologic techniques are available to aid in the detection and diagnosis of renal masses (eg, see Figures 20–1 through 20–3), high-quality, multiphase (including contrast-enhanced) cross-sectional imaging (CT and MRI) is the gold standard (Wang et al, 2018). Ultrasound of renal masses plays a role in surveillance of cysts or active surveillance of solid masses in select patients. Routine **positron emission tomography (PET)** imaging has limited utility, but use of alternate radiotracers is an area of active research (Elahmadawy et al, 2018). Some investigators have shown sestamibi imaging to have some value in differentiating oncocytoma from renal cell carcinoma, but this remains experimental (Gorin et al, 2016).



▲ **Figure 20–2.** Computed tomogram of an angiomyolipoma (*arrows*).



▲ **Figure 20–3.** Photomicrograph of clear cell renal adenocarcinoma (original magnification, ×125).

A. Imaging Classification for Renal Lesions

The Bosniak classification for complex renal cysts was initially described in 1986 and most recently updated in 2005 (Table 20–1) (Israel and Bosniak, 2005; Bosniak, 1986; Muglia and Westphalen, 2014). Cystic lesions are classified according to cyst wall thickness, septations, enhancement, nodularity, calcifications, and fluid density. Higher cyst classification correlates with increased likelihood of renal malignancy. Bosniak I–II lesions do not require additional follow-up, Bosniak IIF lesions require initial short-term (6-month) reimaging with annual imaging for 5 years, and patients with Bosniak III–IV lesions should be counseled about active surveillance or treatment.

For solid renal lesions, scoring systems can standardize the reporting of tumor size and complexity and are useful for standardized comparisons in research. The RENAL nephrometry score and PADUA score are based on tumor size, exo- or endophytic nature, nearness to collecting system, renal sinus or hilum, location relative to renal polar lines, and anterior/posterior nature (Table 20–2) (Kutikov and Uzzo, 2009; Ficarra et al, 2009). In both scoring systems, a higher score denotes a more surgically complex mass.

Table 20–1. Bosniak classification system for renal cysts.

Bosniak rank	Cyst features on contrast-enhanced CT	Likelihood of malignancy (%)
I	Thin margins, homogeneous with cystic fluid matching water density (0–20 HU), sharp delineation with renal parenchyma	<3
II	Thin margins, one or a few thin septations, small/fine calcifications, or hyperdense cysts up to 3.0 cm (60–70 HU)	0–18
IIF	Multiple septations, or walls/septations with nodular or irregular calcifications, or hyperdense cysts ≥3.0 cm or with only 25% of cyst wall visible	>18
III	Thick-walled cystic lesion, irregular septations, with heterogeneity in septum, wall, or cyst contents; large or irregular nodules with measurable enhancement	33–50
IV	Any cystic lesion with solid components	>90

Data from Israel GM, Bosniak MA: An update of the Bosniak renal cyst classification system. Urology 2005 Sep;66(3):484–488; Muglia VF, Westphalen AC: Bosniak classification for complex renal cysts: History and critical analysis. Radiol Bras 2014 Nov-Dec;47(6): 368–373.

B. Ultrasonography

Ultrasound examination is a noninvasive, relatively inexpensive technique able to further delineate a renal mass. It is approximately 98% accurate in distinguishing simple cysts from solid lesions. Strict ultrasonographic criteria for a simple cyst include through transmission, a well-circumscribed mass without internal echoes, and adequate visualization of a strong posterior wall (Figure 20–4). Contrast-enhanced ultrasound using microbubbles, rather than a contrast agent, can better visualize renal parenchyma and blood flow within and around the tumor. This is useful in patients who may not receive contrast because of a severe allergy or chronic kidney disease (Bertolotto et al, 2018). Renal ultrasound is also useful for surveillance of complex cysts or solid masses after they have been initially characterized by CT or MRI.

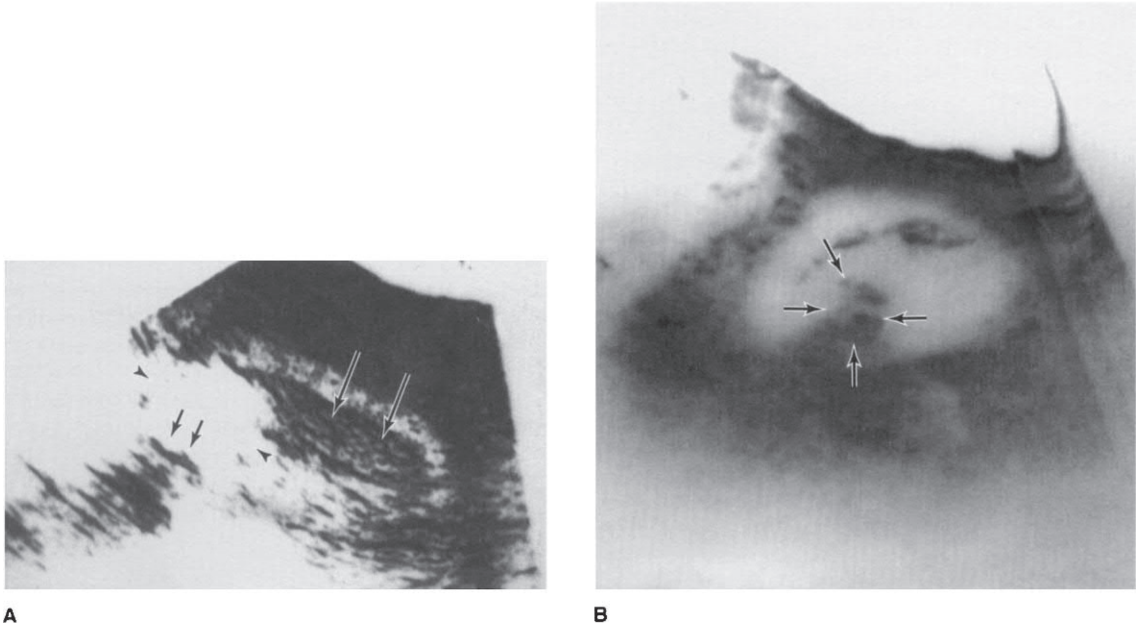
C. CT Scanning

A typical finding of RCC on CT is a mass that is enhanced with the use of intravenous contrast media. In general, RCC exhibits an overall decreased density in Hounsfield units compared with normal renal parenchyma but shows either a homogeneous or heterogeneous pattern of enhancement (increase in density of >20 Hounsfield units) following contrast administration (Figure 20–5) (Wang et al, 2018). CT can also identify macroscopic fat in a renal mass (< -0 HU), indicating an angiomyolipoma (Figure 20–6). In addition to defining the primary lesion, CT scans also stage the patient by visualizing the renal hilum, perinephric space, renal vein and vena cava, adrenal glands, regional lymph nodes, and adjacent organs. A CT scan of the chest is indicated in patients with equivocal chest x-ray findings. Patients who present with symptoms consistent with brain metastases should be evaluated with either head CT or MRI. Intraoperative ultrasonography is also often used to confirm the extent and number of masses in the kidney at the time of performing a partial nephrectomy.

Table 20–2. RENAL and PADUA scoring systems for renal mass surgical complexity.

RENAL score		PADUA score	
Feature	Points	Feature	Points
Radius ≤4 cm 4–7 cm >7 cm	 1 2 3	Size ≤4 cm 4–7 cm >7 cm	 1 2 3
Endo/exophytic ≥50% exophytic <50% exophytic Endophytic	 1 2 3	Endo/exophytic ≥50% exophytic <50% exophytic Endophytic	 1 2 3
Nearness to collecting system/renal sinus ≥7mm >4 and <7 mm <4 mm	 1 2 3	Renal sinus Not Involved Involved	 1 2
Longitudinal polar location Entirely above or below polar line Crosses polar Line >50% of mass is across polar line or mass crosses the axial renal midline or mass is entirely between the polar lines	 1 2 3	Longitudinal polar location Superior/inferior Middle	 1 2
		Urinary collecting system Not Involved Involved	 1 2
Touches renal hilum	h	Renal rim Lateral Medial	 1 2
Anterior/psterior	a/p	Anterior/Posterior	a/p

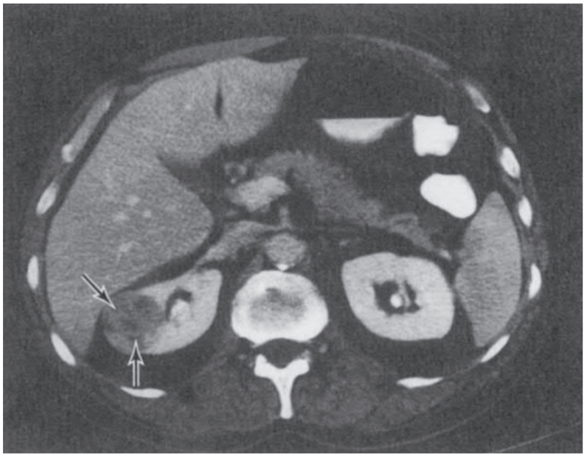
PADUA = preoperative aspects and dimensions used for an anatomical (classification); RENAL = radius, exophytic or endophytic, nearness to collecting system or sinus, anterior or posterior, and location relative to polar lines.



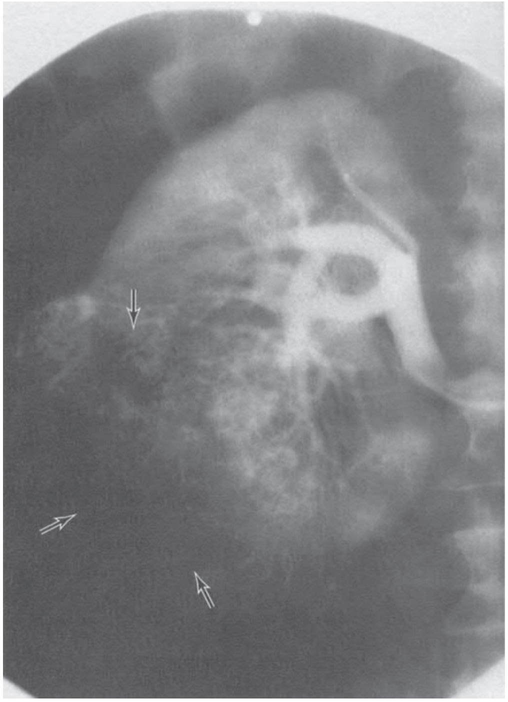
▲ **Figure 20–4.** ***A:*** Ultrasound image of a simple renal cyst showing renal parenchyma (*long arrows*), cyst wall (*arrowheads*), and a strong posterior wall (*short arrows*). ***B:*** Ultrasound image of a solid renal mass (*arrows*).

D. Magnetic Resonance Imaging

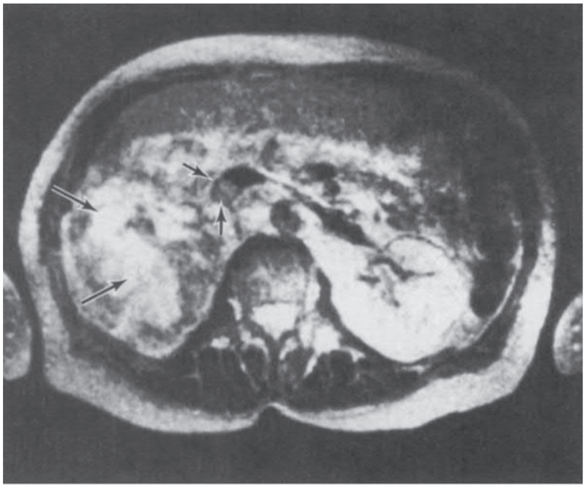
On MRI, renal masses are isointense to moderately hypointense on T1-weighted phases and typically hyperintense on T2-weighted phases. MRI is generally equivalent to CT for visualizing renal masses (Leveridge et al, 2010). Its primary advantage is in the evaluation of patients with suspected



▲ **Figure 20–5.** Computed tomogram (contrast enhancement) of a renal cell carcinoma (*arrows*).



▲ **Figure 20–6.** Right renal angiogram showing typical neovascularity (*arrows*) in a large lower pole renal cell cancer.



▲ **Figure 20–7.** Transaxial magnetic resonance image (T2) of a renal cell carcinoma (*long arrows*) with vena caval tumor thrombus (*short arrows*).

macroscopic fat or renal vein and vena cava involvement with tumor thrombus (Figure 20–7) (Aslam Sohaib et al, 2001). The use of gadolinium-based contrast in MRI can avoid the risks of contrast nephropathy seen with iodinated contrast in patients with renal insufficiency. However, in those with severe renal insufficiency (eGFR < 30 mL/min), there is a significant risk of nephrogenic systemic fibrosis with gadolinium. The primary disadvantage of MRI is higher cost, longer duration, and patient discomfort during the study.

E. Radionuclide Imaging

Determination of metastases to bones is most accurate by radionuclide bone scan, although the study is nonspecific and requires confirmation with bone x-rays of identified abnormalities to verify the presence of the typical osteolytic lesions. A bone scan should be considered in patients with an elevated alkaline phosphatase and otherwise normal liver function tests. There is a very low incidence of bone metastasis with normal alkaline phosphatase and it is not routinely necessary (Henriksson et al, 1992).

F. Positron Emission Tomography (PET) and Targeted Imaging

This technique allows the measurement of systemically administered radionuclides that can preferentially accumulate in cancer cells. Most recent studies suggest that fluorodeoxyglucose (FDG)-PET is of insufficient sensitivity to be useful for staging RCC (Elahmadawy et al, 2018). However, PET scans with alternate radionuclides, such as ^{11}C-choline and prostate-specific membrane antigen (PSMA)-targeted ^{18}F-DCFPyL, show potential for identifying metastatic RCC in early research (Nakanishi et al, 2018; Gorin et al, 2017; Rowe et al, 2015).

Biopsy of Renal Masses

The role of renal mass biopsy is rapidly evolving as additional risk stratification becomes an important part of management in patients undergoing active surveillance for renal masses. According to the 2017 American Urological Association Guidelines for Localized Kidney Cancer, renal mass biopsy should be considered if a mass is concerning for metastatic, hematologic, infectious, or inflammatory etiology and should not be considered in otherwise young and healthy patients that would undergo intervention anyway or older, frail patients that are not planning to undergo intervention (Campbell et al, 2017). Other settings in which biopsy may be appropriate include establishing a diagnosis in patients who are not surgical candidates, selecting patients undergoing active surveillance for small renal masses, and evaluating radiographically indeterminate lesions. Biopsy should be considered primarily in those patients in whom the results would change management. Core biopsy is more sensitive and specific than fine-needle aspiration and is preferred. In a large systematic review, the overall non-diagnostic rate was 14.1% after initial biopsy, and repeat biopsy leading to a diagnosis in 80% of the remaining patients (Patel et al, 2016). There have been no reported cases of tumor seeding in the contemporary literature. Approximately 8% of all patients undergoing renal mass biopsy experience a direct complication, such as benign hematomas (5%), significant pain (1%), pneumothorax (<1%), gross hematuria (<1%), and need for transfusion (rare) (Patel et al, 2016).

Differential Diagnosis

When a patient presents with clinical findings consistent with metastatic disease and is found to have a renal mass, a diagnosis of RCC can be straightforward. Most patients present with a renal mass discovered after an evaluation of hematuria or pain or as an incidental finding during an imaging workup of an unrelated problem. The differential diagnosis of RCC includes other solid renal lesions. The great majority of renal masses are simple cysts. Once the diagnosis of a cyst is confirmed by US, no additional evaluation is required if the patient is asymptomatic. Equivocal findings or the presence of calcification within the mass warrant further evaluation by CT. A wide variety of pathologic entities appear as solid masses on CT scans, and differentiation of benign from malignant lesions is frequently difficult. Findings on CT scan that suggest malignancy include amputation of a portion of the collecting system, presence of calcification, a poorly defined interface between the renal parenchyma and the lesion, invasion into perinephric fat or adjacent structures, and the presence of abnormal periaortic adenopathy or distant metastatic disease. The frequency of benign lesions among renal masses <7 cm in size is as high as 16–20% (Snyder et al, 2016; Duchene et al, 2003). Masses >7 cm are rarely benign.

Some characteristic lesions can be defined using CT criteria in combination with clinical findings. Angiomyolipomas (with large fat components) can easily be identified by the low-attenuation areas classically produced by substantial fat content. A renal abscess may be strongly suspected in a patient presenting with fever, flank pain, pyuria, and leukocytosis, and an early needle aspiration and culture should be performed. Other benign renal masses (in addition to those previously described) include granulomas and arteriovenous malformations. Renal lymphoma (both Hodgkin's disease and non-Hodgkin's disease), transitional cell carcinoma of the renal pelvis, adrenal cancer, and metastatic disease (most commonly from a lung or breast cancer primary) are additional diagnostic possibilities that may be suspected based on CT and clinical findings.

RENAL CELL CARCINOMA

Epidemiology

Renal cell carcinoma (RCC) accounts for 2–5% of adult cancers and constitutes approximately 70% of all primary malignant renal tumors (Siegel et al, 2018; Gansler et al, 2018). There has been an increase in the incidence of all stages of RCC over the past few decades, but age-standardized mortality rates have remained stable (Znaor et al, 2015). RCC occurs most commonly in the sixth to seventh decades and has a male:female ratio of 2:1 (Scelo et al, 2018).

Etiology

Renal cell carcinoma is a heterogenous disease with multiple exposure-related and genetic etiologies, such as mutations along metabolic and hypoxia-related pathways. Male sex, obesity, and increasing age are also significantly associated with development of RCC (Lotan et al, 2016). Cigarette smoking is the only risk factor consistently linked to RCC by both epidemiologic case–control and cohort studies (La Vecchia et al, 1990), with most investigations demonstrating nearly a twofold increase in risk for the development of RCC in smokers. Analysis of a large, prospective screening trial showed a hazard ratio of 1.88 for development of RCC in current smokers with a >50-pack/year history compared to never smokers (Lotan et al, 2016). A meta-analysis of retrospective data showed a relative risk of developing RCC of 1.45 in current smokers and 1.21 in former smokers (Hunt et al, 2005). Occupational exposures, to toxins such as asbestos, solvents, and cadmium, have been associated with increased risk for RCC (Mandel et al, 2018).

Acquired cystic disease of the kidneys is a well-recognized entity of multiple bilateral cysts in the native kidneys of uremic patients (Reichard et al, 198). The risk of developing RCC has been estimated to be >30 times higher in patients receiving dialysis who have cystic changes in their kidneys than in the general population (Brennan et al, 2018). Several series reported in the literature suggest that RCC occurs in 3–9% of patients with acquired cystic disease of the kidneys (Gulanikar et al, 1998).

Pathology

Renal cell carcinoma originates from the proximal renal tubular epithelium, as evidenced by electron microscopy and immunohistochemical analysis (Wilkerson et al, 2014; Mackay et al, 1987). These tumors occur with equal frequency in either kidney and are randomly distributed in the upper and lower poles. RCCs originate in the cortex and tend to grow out into perinephric tissue, causing the characteristic bulge or mass effect that aids in their detection by diagnostic imaging studies. Grossly, the tumor is characteristically yellow to orange because of the abundance of lipids, particularly in the clear cell type. RCCs do not have true capsules but may have a pseudocapsule of compressed renal parenchyma, fibrous tissue, and inflammatory cells.

Histologically, RCC is most often a mixed carcinoma containing clear cells, granular cells, and, occasionally, sarcomatoid-appearing cells. The classifications of the subtypes of RCC are based on morphology and cytogenetic characteristics. Most RCCs are classified into one of the following histologic subtypes: conventional clear cell, papillary (chromophilic) types 1 and 2, clear cell papillary, chromophobe, collecting duct, renal medullary, translocation, neuroendocrine, and with sarcomatoid features (Wilkerson et al, 2014). Benign renal tumors are papillary adenoma, renal oncocytoma, and metanephric adenoma. Clear cells are rounded or polygonal with abundant cytoplasm, which contains cholesterol, triglycerides, glycogen, and lipids (Figure 20–3).

The cells present in the papillary (chromophilic) type contain less glycogen and lipids, and electron microscopy reveals that the granular cytoplasm contains many mitochondria and cytosomes. Chromophobe-type carcinomas contain large polygonal cells with distinct cell borders and reticulated cytoplasm, which can stain diffusely with Hale's colloidal iron (Thoenes et al, 2018). Oncocytic RCC andoncocytomas tend to have cytoplasm packed with mitochondria, giving it a granular appearance. Collecting duct tumors tend to have irregular borders and a basophilic cytoplasm with extensive anaplasia and are likely to invade blood vessels and cause infarction of tissue. Sarcomatoid cells are spindle-shaped and form sheets or bundles. This latter cell type rarely occurs as a pure form and is most commonly a component of either the clear cell or papillary cell type (or both).

Familial Syndromes

Many hereditary forms of RCC have been described, which have deepened our understanding of the genetic causes and pathways involved in RCC (Linehan and Ricketts, 2013). **Von Hippel–Lindau disease** is a familial cancer syndrome in which affected individuals present with clear cell RCC, central nervous system (CNS) hemangiomas, retinal agniomas, and pheochromocytoma. Initially isolated to a mutation on chromosome 3p, in 1993 Latif and colleagues identified the von Hippel–Lindau (VHL) gene (Zbar et al, 1987; Latif et al, 1993). The germline mutation has been detected in approximately 75% of families affected by von Hippel–Lindau disease and at least 50% of cases of sporadic clear cell RCC (Latif et al, 1993; Chen et al, 1995). VHL is a tumor suppressor gene, the product of which binds to ubiquitin to sequester and degrade hypoxia-inducible factor (HIF). In the absence of VHL, HIF accumulates, leading to a hypermetabolic state and increased angiogenesis.

Hereditary papillary renal carcinoma was described in 1994 and is characterized by a predisposition to develop multiple bilateral renal tumors with a papillary histologic appearance (Zbar et al, 1994). It is due to a mutation in c-MET, a receptor tyrosine kinase that mediates cellular pathways associated with proliferation and cell motility (Organ and Tsao, 2011; Schmidt et al, 1997). In contrast to manifestations in von Hippel–Lindau patients, the major neoplastic manifestations appear to be confined to the kidney, presenting with type 1 papillary RCC.

Hereditary leiomyomatosis is caused by a mutation in the fumarate hydrate (FH) gene, which catalyzes conversion of fumarate to malate in the Krebs cycle. Patients develop type 2 papillary RCC, cutaneous leiomyomas, and uterine leiomyomas (Toro et al, 2003; Zinn et al, 1986).

Succinate dehydrogenase kidney cancer (SDH-RCC) is caused by a mutation in any of three succinate dehydrogeanse subunits, B, C, or D. Succinate dehydrogenase, also part of the Krebs cycle, catalyzed the conversion of succinate to fumarate. Patients develop clear cell RCC, chromophobe RCC, type 2 papillary RCC, and oncocytomas.

Birt–Hogg–Dubé syndrome is caused by a mutation in the folliculin gene (FLCN) and is associated with chromophobe clear cell RCC, hybrid oncocytic/chromophobe tumors, spontaneous pneumothorax, lung cysts, and cutaneous fibrofolliculomas (Toro et al, 1999; Nickerson et al, 2002).

Tuberous sclerosis (caused by TSC1/2 genes) is associated with AMLs, clear cell RCC, seizures, and developmental delay (Bissler and Christopher Kingswood 2018; Anonymous, 1993).

Pathogenesis

Renal cell carcinomas are vascular tumors that tend to spread either by direct invasion through the renal capsule into perinephric fat and adjacent visceral structures or by direct extension into the renal vein. Approximately 20–25% of patients show evidence of metastatic disease at presentation. The most common site of distant metastases is the lung. However, liver, bone (osteolytic), ipsilateral adjacent lymph nodes and adrenal gland, brain, the contralateral kidney, and subcutaneous tissue are frequent sites of disease spread.

Tumor Staging and Grading

A. Tumor Staging

The ultimate goal of staging is to select appropriate therapy and obtain prognostic information. Appropriate studies for a complete clinical staging evaluation include history and physical examination, complete blood count, serum chemistries (renal and hepatic function), urinalysis, chest x-ray (chest CT scan for an equivocal exam), CT or MRI of abdomen and pelvis, and a radionuclide bone scan (with x-rays of abnormal areas) if the patients have symptomatic bone pain or elevated alkaline phosphatase.

The tumor–node–metastasis (TNM) system classifies the extent of tumor involvement and is currently the system that is most frequently used. The TNM classification system for RCC has undergone multiple revisions; the most recent edition is the 2017 version (Table 20–3) (Amin, 2017; Paner et al, 2018).

Table 20–3. Tumor–node–metastasis staging system.

T	Primary tumor
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor ≤ 7 cm in greatest dimension, limited to kidney
pT1a	Tumor ≤ 4 cm in greatest dimension, limited to kidney
pT1b	Tumor > 4 cm but ≤ 7 cm in greatest dimension limited to kidney
pT2	Tumor > 7 cm in greatest dimension, limited to kidney
pT2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to kidney
pT2b	Tumor > 10 cm, limited to kidney
pT3	Tumor extends into major veins or perinephric tissues, but not into ipsilateral adrenal gland and not beyond Gerota's fascia
pT3a	Tumor extends into renal vein or its segmental branches, invades pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
pT3b	Tumor extends into vena cava below diaphragm
pT3c	Tumor extends into vena cava above diaphragm or invades wall of vena cava
pT4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
N	**Regional lymph nodes**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in regional lymph node(s)
M	**Distant metastasis**
pMx	Distant metastasis cannot be assessed
pM0	No distant metastasis
pM1	Distant metastasis

Data from the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (eds.): *AJCC Cancer Staging Manual,* 8th Ed. Springer New York, 2017.

B. Tumor Grading

Historically, the four-level Fuhrman grading system, based on nuclear size, irregularity, and nucleolar prominence, was used to grade renal cell carcinoma (Fuhrman et al, 1982). More recently, the 2016 World Health Organization and International Society of Urologic Pathology consensus recommendation has kept a four-tiered system, but grades 1–3 depend on increasing nucleolar prominence (magnification at which it can be detected), and grade 4 is based on presence of nuclear pleomorphism, tumor giant cells, and/or rhabdoid/sarcomatoid differentiaton (Delahunt et al, 2013; Moch et al, 2016). Of note, this grading system is applicable only to clear cell and papillary renal cell carcinoma, as it has not yet been validated in other histologic subtypes.

Treatment of Localized Disease

Management options for small cT1a (<4-cm) localized renal cell carcinoma include active surveillance (for masses < 3 cm), surgical resection (partial or radical nephrectomy), and percutaneous thermal ablation. Treatment selection is driven by tumor size/stage, location, preservation of noninvolved renal parenchyma, preexisting patient comorbidity, surgical risk, and patient preference. For masses larger than 4 cm (cT1b and above), surgical resection is the standard of care.

A. Active Surveillance

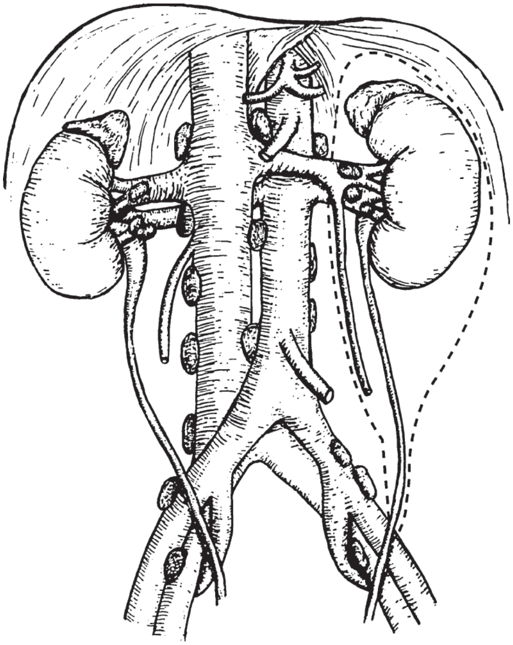
Small renal masses, defined as being under 3 cm, are known to have a low growth rate and rare rate of metastatic spread. In patients with small renal masses that remain on active surveillance with long-term follow-up, the rate of growth is between 1 and 2 mm per year (Uzosike et al, 2018; McIntosh et al, 2018). At 5 years, approximately 1 in 5 patients can safely avoid intervention, and in a cohort of 457 patients followed for a median of 63 months, only one patient developed metastatic disease (McIntosh et al, 2018). Consequently, AUA guidelines support surveillance of small renal masses in patients with significant comorbidity where the competing risks of other-cause mortality outweight the risks of intervention. Surveillance regimens consist of baseline cross-sectional imaging followed by renal ultrasound every 6–8 months. Intervention is recommended in patients with a growth rate over 5 mm per year or absolute size greater than 3 cm (Campbell et al, 2017).

B. Thermal Ablation

Various thermal ablative options exist for treatment of small renal masses (<3 cm), including cryoablation, radiofrequency ablation, and microwave ablation (Shin et al, 2016). There are currently no dead-to-head data that can be used to recommend one treatment modality over another, but AUA guidelines recommend percutaneous ablation (Campbell et al, 2017). While there are no randomized data, retrospective studies comparing partial nephrectomy and ablative approaches indicate lower local recurrence-free survival for patients undergoing partial nephrectomy (HR 0.37, 95% CI 0.15–0.89) with a single treatment, but no difference when allowing for a second, salvage ablation (Pierorazio et al, 2016). Thermal ablation can be considered as an effective nephron-sparing approach in patients with significant comorbidities, obesity, a solitary kidney, or advanced age.

C. Surgical Resection

Surgical removal of the early-stage lesion remains the gold-standard therapy for RCC patients. Appropriate therapy depends almost entirely on the stage of tumor at presentation and therefore requires a thorough staging evaluation. Minimally invasive approaches (laparoscopic or robot-assisted laparoscopic partial nephrectomy, or laparoscopic radical nephrectomy) are preferred if technically feasible, because of the shorter patient recovery times compared to open approaches. The goal of partial nephrectomy is to achieve the removal of tumor with negative margins while minimizing ischemia time and preserving normal renal parenchyma. An open approach may be favored for large or complex masses, or in the case of solitary kidney. Formally, radical nephrectomy entails en bloc removal of the kidney and its enveloping fascia (Gerota's), including the ipsilateral adrenal, proximal one-half of the ureter, and lymph nodes up to the area of transection of the renal vessels (Figure 20–8). However, unless it



▲ **Figure 20–8.** Boundaries of a left radical nephrectomy. Dotted line represents both the surgical margin and Gerota's fascia.

is directly involved by tumor or harbors a metastatic lesion, the adrenal gland can be spared. Historically, between 18% and 33% of patients undergoing radical nephrectomy with lymph node dissection for RCC had metastatic disease identified (Skinner, 1983). However, with improved imaging, stage migration and early detection, the benefit for routine lymphadenectomy in clinically node-negative patients became less clear. EORTC 30881 randomized patients with RCC to undergo radical nephrectomy with or without lymphadenectomy. Only 4% were noted to have unsuspected lymph node metastasis, and there were no differences in overall survival, time to progression, and recurrence-free survival between the two groups (Blom et al, 2009; Leibovich and Blute, 2008).

When deciding between radical and partial nephrectomy for resection of renal masses, the main goals are to maximize oncologic outcomes, protect renal function, and minimize surgical morbidity. American Urological Association guidelines for localized kidney cancer recommend prioritizing partial nephrectomy for cT1a masses, solitary kidney, bilateral tumors, familial RCC conditions, preexisting chronic kidney disease, and proteinuria, and to consider nephron-sparing approaches for patients who are young, have multifocal masses, or significant comorbidities that will have a detrimental impact on renal function (Campbell et al, 2017). Radical nephrectomy should be considered for those with more aggressive tumors (suggested by either clinical stage or histologic grade) if partial nephrectomy would be technically complex, there were no preexisting chronic kidney disease, *and* normal contralateral renal function with postoperative eGFR were expected to be over 45 (Campbell et al, 2017).

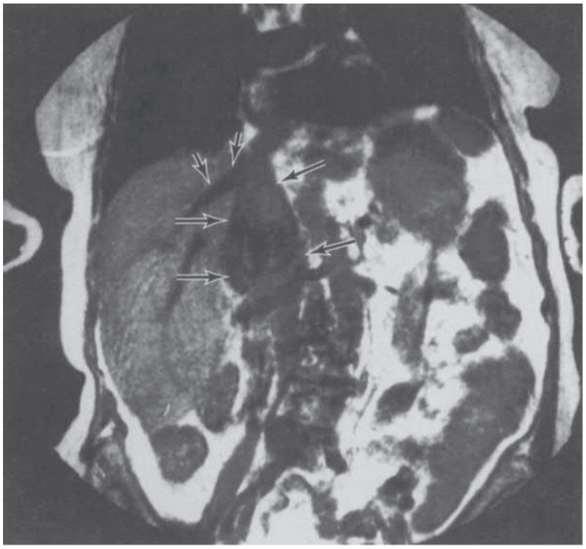
In a prospective randomized control trial comparing partial nephrectomy to radical nephrectomy in patients with masses <5 cm (EORTC 30904), there was improved overall survival in patients undergoing radical nephrectomy compared to partial nephrectomy, in the intention-to-treat analysis. However, when limited to the cohort of patients with RCC, no difference in cancer-specific survival between the two treatment approaches was identified (Van Poppel et al, 2011). The study suffered from low accrual and was terminated prematurely, and it was therefore underpowered. The trial was also critized as partial nephrectomies were performed by generally lower-volume surgeons, potentially biasing outcomes. For larger tumors, retrospective data has shown similar cancer control rates between partial and radical nephrectomy, but these data must be interpreted in light of significant selection bias and confounding due to age and comorbidities (Crépel et al, 2010; Badalato et al, 2012; Meskawi et al, 2014; Hansen et al, 2012; Kopp et al, 2014; Long et al, 2012; Maddox et al, 2015; Joniau et al, 2009; Leibovich et al, 2004; Gershman et al, 2018). In a comprehensive meta-analysis of 21 retrospective studies and over 11,000 patients, compared to those undergoing radical nephrectomy, patients undergoing partial nephrectomy are likely to be younger, have smaller masses, lower rates of tumor recurrence, lower cancer-specific mortality, and lower all-cause mortality (Mir et al, 2017).

The oncologic goal is resection with a negative surgical margin. However, the size of negative margin is not significant, allowing for the resection of minimal normal renal parenchyma. The positive margin rates vary by approach; in a large retrospective analysis of administrative data the positive margin rates in partial nephrectomy are 4.9% for open, 8.1 for laparoscopic, and 8.7% for robot-assisted partial nephrectomy (Tabayoyong et al, 2015). The rate of recurrence was found to be approximately 2 times higher in patients with a positive surgical margin, but this was not associated with the site of recurrence (local or distant), and in stratified analyses a positive margin was associated with recurrence in high-risk tumors but not in low-risk tumors (Shah et al, 2016).

The second goal of surgical resection is to protect renal function and spare noninvolved renal parenchyma when possible. In this context, the causes of chronic kidney disease (CKD) can be divided into through broad categories, CKD due to preexisting medical conditions, CKD caused by removal or damage to nephrons during treatment for renal masses, and CKD due to medical comorbidities that develop after surgery. During treatment, nephron loss can be due to the volume of resected normal renal parenchyma or ischemia induced during clamping of the renal artery. To minimize these impacts, surgeons opt for partial nephrectomy when technically feasible for appropriate masses with minimal additional normal renal parenchyma resected and to keep renal artery clamp times low. Traditionally, a cutoff of less than 30 minutes of ischemia time has been recommended, but a simple dichotomous cutoff is likely too simplistic (Mir et al, 2018). Partial nephrectomy with cold ischemia time (in open cases), or without arterial clamping, with superselective arterial clamping, and with early unclamping have been described. Overall, it appears that in patients undergoing partial nephrectomy, the annual decline in renal function in those with preexisting medical comorbidities is approximately 5% per year, while in those with de-novo surgical CKD it is 0.7% per year (Lane et al, 2013).

The third goal is to minimize patient peri-operative morbidity. Partial nephrectomy is more technically complex and is associated with higher perioperative complication rates, including bleeding, and urine leak, and higher readmission rates (Van Poppel et al, 2011; Odisho et al, 2018). Increasing tumor complexity, as measured by the RENAL score, is associated with a higher rate of major complicaitons within 30 days, but no differences in minor complications were noted (Simhan et al, 2012). These risks must be weighed with the potential benefits of partial nephrectomy.

Preoperative renal artery embolization (angioinfarction) has been used in the past as a surgical adjunct to facilitate radical nephrectomy, but because there is no conclusive evidence that preoperative embolization actually decreases blood loss or facilitates surgery, its use should be limited to select patients with very large tumors in which the renal artery may be difficult to reach early in the procedure. In addition, this technique may be useful to palliate patients



▲ **Figure 20–9.** Coronal magnetic image (T1) of a large vena caval tumor thrombus (*long arrows*) in a patient with renal cell carcinoma. Thrombus extends just to entrance of hepatic veins (*short arrows*).

with nonresectable tumors and significant symptoms such as hemorrhage, flank pain, or paraneoplastic syndromes.

In a large population-based analysis, 9% of patients presenting with RCC had some degree of vena caval involvement (Figure 20–9) (Whitson et al, 2013). While the presence of tumor thrombus represents a combination of late diagnosis and more aggressive underlying tumor biology, once tumor is beyond the renal vein, the extent of thrombus does not appear to portend worse cancer-specific survival (Whitson et al, 2013; Wagner et al, 2009). The surgical approach to the removal of caval thrombi depends entirely on the level of cephalad extension. In general, these thrombi do not invade the wall of the cava and therefore can be removed without resection of the caval wall. For tumor thrombi that have reached the level of the right atrium, the use of cardiopulmonary bypass is typically required.

The approach to the patient with either bilateral RCC or disease in a solitary kidney differs from the standard approach of radical nephrectomy. Radical nephrectomy in these patients or in those with solitary kidneys obviously commits patients to long-term dialysis or renal transplantation and the morbidities of these conditions. Staging these patients is essentially the same as previously outlined, with the notable exception that either MR or CT angiography may be used to assess the extent of tumor within the kidney and the renal artery anatomy. Surgical alternatives to radical nephrectomy include open or laparoscopic/robotic partial nephrectomy, ex vivo partial nephrectomy, and enucleation of multiple lesions (Novick et al, 1980). Given the lack of curative adjuvant therapy, the risk of inadequate excision, and subsequent recurrence from various kidney-sparing approaches, partial nephrectomy with an adequate parenchymal margin remains the preferred treatment.

D. Adjuvant Treatment for Localized Disease

While the administration of systemic therapy after surgical resection plays an important role in many oncological settings, current data from randomized trials do not support its routine use in renal cell carcinoma. The ASSURE trial randomized patients to adjuvant sunitinib, sorafenib, or placebo after complete surgical resection and identified no difference in disease free survival (Haas et al, 2016). The PROTECT trial randomized patients pazopanib or placebo, and the ATLAS trial randomized patients to axitinib or placebo after nephrectomy, with neither of them identifying a disease free survival benefit (Gross-Goupil et al, 2018; Motzer et al, 2017). The S-TRAC study randomized a higher-risk cohort (pT3+) patients to sunitinib or placebo after nephrectomy and did identify a disease free survival benefit (6.8 vs 5.6 years, $p < .03$) (Ravaud et al, 2016). Despite some conflicting results, the evidence does not support adjuvant treatment for localized disease at this time.

E. Follow-up Care

Surveillance of patients with localized renal cell carcinoma after definitive treatment consists of routine history and physical exams, laboratory evaluation, and imaging, with frequency on the basis of their disease stage and treatment. American Urological Association guidelines recommend "routine" H&P, CBC, serum chemistries, and urinalysis (assessing for proteinuria) in all patients after treatment, but the exact frequency is not specified and should be adjusted to match each patient's unique clinical scenario (Donat et al, 2013). All patients should undergo a chest x-ray annually for 3 years. Patients with pT1 masses who go for a partial nephrectomy should have some form of abdominal imaging (CT, MRI, or US) at 3–12 months and annually for 3 years, whereas additional imaging beyond the first year is optional for those that undergo radical nephrectomy. For higher-risk masses (pT2-4), initial cross-sectional imaging (CT, MRI) is recommended at 3–6 months postoperatively, followed by abdominal imaging (CT, MRI, or US) and chest x-ray every 6 months for 3 years and annually for 2 additional years. There are significant costs and radiation exposure associated with long-term surveillance, and some have proposed a more granular risk-based approach, which may inform future guidelines (Lobo et al, 2016; Stewart-Merrill et al, 2015).

▶ Treatment of Disseminated Disease

Approximately 20–25% patients with RCC will present with advanced disease, and of the remainder that present with localized disease, approximately 30% will go on to develop recurrence (Dabestani et al, 2016; Speed et al, 2017). There has been a rapid growth in the understanding of kidney cancer biology, matched by a proliferation of systemic treatment options.

Prior to 2005, there were two approved treatments for metastatic kidney cancer. Since then, 12 new agents across various mechanistic pathways, such as the vascular endothelial growth factor (VEGF) pathway, mammalian target of rapamycin (mTOR) pathway, and immune checkpoint blockage have been approved and demonstrated significantly longer survival for patients with metastatic renal cell carcinoma.

A. Risk Stratification

Selecting the most appropriate treatment of patients with metastatic renal cell carcinoma hinges on accurate risk stratification. Current risk stratification models rely on factors such as histology, patient performance status, and various common laboratory values, but molecular and genetic approaches to more accurately target therapy are under investigation (Graham et al, 2018). The Memorial Sloan Kettering Cancer Center (MSKCC) model, based on patients treated during the immune-therapy (pre-2005), stratified patients into good (no risk factors), intermediate (one or two risk factors), and poor risk (three or more risk factors), based on performance status, time from initial diagnosis to initiation of systemic treatment, lactate dehydrogenase (LDH), serum calcium, and hemoglobin levels (Motzer et al, 2002). Patients are assigned one point each for hemoglobin below lower limit of normal, calcium >10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, Karnofsky performance status below 80, and time from diagnosis to treatment < 1 year. The International Metastatic Kidney Cancer Database Consortium (IMDC) model does not use lactate dehydrogenase but instead adds neutrophils above upper limit of normal and platelets above upper limit of normal. Median overall survival is 43 monhts in good risk, 23 months in intermediate risk, and 8 months in poor-risk patients (Heng et al, 2009, 2013).

B. Surgery for Metastatic Disease

1. Cytoreductive nephrectomy—The role of radical nephrectomy in the management of patients with advanced disease has been reevaluated on the basis of the results of randomized clinical trials. Historically, radical nephrectomy was primarily used as a palliative procedure in the setting of metastatic disease for managing patients with severe hemorrhage or unremitting pain. During the cytokine era (pre-2005), retrospective observations of the potential for nephrectomy to improve the outcome of patients receiving biologic response modifier therapy prompted a prospective evaluation of this effect. Two randomized clinical trials (SWOG 8949 and EORTC 30947) randomized patients with advanced RCC to nephrectomy followed by interferon-alpha (IFN-α) 2b versus interferon alone (Mickish et al, 2001; Flanigan et al, 2001). Both studies reported a survival advantage in the group receiving IFNα and surgery compared to IFNα alone, and in combined analysis the median survival benefit was 5.8 months (Flanigan et al, 2004). These two studies prompted a shift in the standard of care for patients with metastatic RCC and good performance status who desire systemic therapy to include a nephrectomy prior to systemic therapy.

The continued role of cytoreductive nephrectomy prior to systemic therapy has undergone considerable scrutiny after 2004, with the availability of new targeted systemic therapy (anti-vascular endothelial growth factor (anti-VEGF) tyrosine kinase inhibitors (TKIs) and mTOR inhibitors). Because there was no randomized data to support cytoreductive nephrectomy in these patients, findings from the cytokine era were extrapolated forward. The CARMENA trial, which randomized 450 intermediate and poor-risk patients to treatment with cytoreductive nephrectomy followed by sunitinib to sunitnib alone, published in 2018, found that sunitinib alone was non-inferior to cytoreductive nephrectomy followed by sunitinib for overall survival (Méjean et al, 2018). The benefit of cytoreductive nephrectomy in good-risk patients in the modern era remains unclear and currently enrolling trials may provide guidance.

2. Metastasectomy—Patients presenting with a solitary or oligometastatic renal cell carcinoma may benefit from complete metastasectomy if technically feasible. In a meta-analysis of eight studies including nearly 2300 patients, those that underwent complete metastesectomy, had a median survival of 37–142 months, compared to 8–27 months for those undergoing incomplete metastasectomy (Zaid et al, 2017). While these findings may be confounded by the fact that those with low metastatic burden are more likely to undergo complete resection, there appears to be clinical benefit in appropriately selected patients. In patients who are destined to receive adjuvant therapy, even limited resection of metastases can yield improved survival further emphasizing the potential benefit of tumor debulking (Vogl et al, 2006).

The important role of surgical resection of solitary brain metastases has been highlighted by several randomized trials demonstrating an improvement in survival in patients with solitary brain metastases who undergo both surgical resection and whole-brain radiotherapy compared with patients who receive only radiation therapy (Shuch et al, 2008; Patchell et al, Vecht et al, 1993).

C. Targeted Therapy

There has been significant progress in the development of several antiangiogenic agents and inhibitors of tyrosine kinase and other cell cycle activators in RCC, with nine drugs currently having FDA approval for treatment of metastatic RCC in various settings. VHL is a classic tumor suppressor gene: it binds in complex with other proteins to regulate the degradation of hypoxia-inducible factor-alpha (HIFα). Both inherited and sporadic RCCs may have mutations of the VHL gene resulting in loss of the gene product. This causes increased levels of HIFα, which, in turn, promotes increased expression of various tyrosine kinases, such as vascular endothelial growth factor (VEGF), endothelial derived growth factor (EDGFR), and platelet derived growth factor (PDGFR), which promotes angiogenesis.

Bevacizumab is a monoclonal antibody that binds and inactivates VEGF. It has shown the ability to yield partial responses, delay disease progression, and improve survival in patients with advanced renal cancer (Yang et al, 2003). Randomized trials comparing IFN with the IFN and bevacizumab combination have shown the superiority of the combination in terms of progression-free survival (Escudier et al, 2010; Rini et al, 2010).

Tyrosine kinase inhibitors (TKIs) are small orally bioavailable molecules that block the action of tyrosine kinases, such as VEGF, PDGFR, EDGFR, or hepatocyte growth factor (HGF). Sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib are currently FDA-approved. By blocking the tyrosine kinases, these agents inhibit angiogenesis and lead to cell death. In the first-line setting, sunitinib and pazopanib were shown to have significant activity in the first-line setting with higher response rates and longer progression-free survival compared to IFN or placebo, each showed an improvement of 5–6 months in progression-free survival but minimal benefits in overall survival (Motzer et al, 2007, 2009; Sternberg et al, 2010, 2013). The COMPARZ trial showed that pazopanib was non-inferior to sunitinib for progression-free survivaland overall survival but with less toxicity (Motzer et al, 2013). Subsequently, the CABOSUN trial randomized patients to cabozantinib or sunitinib, which a longer progression free survival in patients receiving cabozantinib (8.2 vs 5.6 months) (Choueiri et al, 2917). One important caveat about these trials is that the majority of patients had clear cell histology and prior nephrectomy. TKIs are generally well tolerated, but patients can experience hepatotoxicity, cardiovascular events, tumor lysis syndrome, thrombotic events, diarrhea, fatigue, hypertension, nausea, poor appetite, abdominal pain, hand–foot syndrome, stomatitis, and mucosal inflammation, among other problems (Sinibaldi et al, 2018).

The mammalian target of rapamycin (mTOR) upregulates HIF, so mTor inhibitors work to downregulate HIF and the downstream TKIs. Temsirolimus was the first mTOR inhibitor to be FDA approved and has been demonstrated to prolong survival in patients with advanced renal cancer who present with poor risk or multiple sites of metastases (Hudes et al, 2007). The phase III trial that demonstrated the efficacy of temsirolimus also notably included several patients with non–clear cell histology, a rare finding in the trials of TKIs. Everolimus was subsequently FDA-approved, based on its ability to prolong progression-free survival as second-line therapy for patients with metastatic clear cell RCC (Motzer et al, 2010). mTOR inhibitors can cause metabolic abnormalities, such as hyperlipidemia and hyperglycemia, along with immunosuppression and noninfection pneumonitis (which can be life-threatening) (Sinibaldi et al, 2018).

D. Immune Therapy

The early benefits of IFNα and IL2 in treating metastatic kidney cancer demonstrates a significant immunologic component of renal cell carcinoma biology. Studies using partially purified human leukocyte interferon in renal cancer were first reported in 1983, with subsequent studies using human lymphoblastoid interferon and, subsequently, recombinant interferon-alpha (r-IFNα). Various doses and schedules of r-IFNα have demonstrated reproducible overall response rates of 10–15% in advanced renal cancer (Pastore et al, 2001). Other large randomized studies have failed to demonstrate a survival advantage of IFNα compared to other biologic response modifiers (Motzer et al, 2000). Interleukin-2 (IL2), a T-cell growth factor, was first identified in 1976. Until 2005, recombinant IL2 was the only agent approved by the FDA for patients with advanced renal carcinoma. The approval was based on several nonrandomized trials showing overall response rates for high-dose IL2 in the 15% range and a complete response rate of 5%, resulting in some long-term survivors being seen with this treatment. The wide variability in response rates to IL2 is likely a function of patient selection. Fyfe and colleagues reported a retrospective evaluation of 255 patients treated with high-dose IL2 and found that an Eastern Cooperative Oncology Group performance score of 0 was a significant predictor of clinical response (Fyfe et al, 1995). With the advent of TKIs and immune checkpoint blockade, these agents are rarely used.

Understanding of the programmed death-1 (PD1)/programmed death ligand 1 (PD-L1) and cytotoxic T–lymphocyte antigen-4 (CTLA-4) pathways has led to the development of new classes of immunotherapy that are having widespread impacts across all cancer treatments. Monoclonal antibodies that target PD1 and PD-L1 may reverse T-cell exhaustion, leading to increased immune function and antitumor activity. CTLA4 appears to be overexpressed on T cells that downregulate immune response, and CTLA4 blockade may downregulate T-reg function and lead to heightened antitumor activity. The CheckMate-214 trial evaluated the combination of ipilimumab (anti-CTLA4 antibody) and nivolumab (anti-PD-1 antibody) compared to sunitinib, and found that while there was no difference in progression-free survival between the two arms, the patients in the immune checkpoint blockade arm (nivo + ipi) experienced longer overall survival (HR 0.68, 95% CI 0.49–0.95) (Motzer et al, 2018).

Given all the drugs available for metastatic RCC in 2018, there are significant challenges in identifying the best way to sequence and/or combine therapy in the first-line or downstream treatment settings. The sequential nature of the treatments also makes it difficult to prove overall survival benefits with each individually used drug in a clinical trial. It is also to be highlighted that much of the clinical benefit seen with the targeted agents is not evidenced by tumor shrinkage (response rates, which are generally modest), but instead from increased duration of tumor control (progression-free survival and projected overall survival) benefits. Finally, in making decisions about which systemic therapy to use for a specific patient, many factors are considered, including performance status, histology, sites and number of metastases, mode of administration, anticipated tolerance to each individual drug, line of therapy, clinical trial options, and patient preferences.

E. Radiation Therapy

Radiation therapy is an important method in the palliation of patients with metastatic RCC. Despite the belief that RCC is a relatively radioresistant tumor, effective palliation of metastatic disease to the brain, bone, and lungs is reported in up to two-thirds of patients (Onufrey and Mohiuddin 1985).

In addition, there is evidence of of an abscopal effect, in which nontargeted metastatic lesions also shrink after radiation to the targeted lesion (Siva et al, 2017; DiBiase et al, 1997; Wang et al, 2017).

BENIGN TUMORS

With the liberal use of computed tomography (CT) scans and magnetic resonance imaging (MRI), benign renal masses are being detected more frequently. Benign renal tumors include, oncocytoma, angiomyolipoma, leiomyoma, lipoma, hemangioma, and juxtaglomerular tumors.

Renal Oncocytoma

Renal oncocytoma is a benign renal tumor that represents an estimated 3–5% of renal masses and affects men more often than women (Romis et al, 2004). Renal oncocytomas generally occur and are contained within a well-defined fibrous capsule. Metastasis is extremely rare, although invasion of the lymphovascular spaces has been observed. On cut section, the surface of the tumor is usually tan or light brown with a central stellate scar, but necrosis typical of renal adenocarcinoma is absent. Composed of large epithelial cells with finely granular eosinophilic cytoplasm (oncocytes), oncocytomas occur in various organs and organ systems including adrenal, salivary, thyroid, and parathyroid glands as well as the kidney (Wobker and Williamson, 2017). The tumors are usually solitary and unilateral, although several bilateral cases and multiple oncocytomas occurring simultaneously (oncocytosis) have been reported (Giunchi et al, 2016; Adamy et al, 2011).

Oncocytomas can also be associated with benign tumors of hair follicles (fibrofolliculomas), colon polyps/tumors, and pulmonary cysts as part of the Birt–Hogg–Dubé syndrome (Toro et al, 1999). The familial renal oncocytoma syndrome has also been described (Lang et al, 2015; Zhan et al, 2018). These patients may have a characteristic genetic abnormality involving a gene located on 17p encoding a protein named **folliculin** (Nickerson et al, 2002).

The diagnosis of oncocytoma is predominantly pathologic because there are no reliable distinguishing clinical characteristics. No characteristic features of the tumors reliably appear on CT, US, or MRI. Oncocytoma is also difficult to distinguish from chromophobe or oncocytic renal cell carcinoma on fine-needle aspiration or core biopsy because of the limited sample and cellular architecture. A recent survey of genitourinary pathologists reported that nearly one-third would not make a definitive diagnosis on biopsy tissue (Williamson et al, 2017).

Angiomyolipoma (Renal Hamartoma)

Angiomyolipomas are benign tumors of the kidney that are characterized by their three major histologic components: mature fat cells, smooth muscle, and blood vessels. Grossly, they are unencapsulated yellow to gray lesions, typically round to oval, that elevate the renal capsule, producing a bulging smooth or irregular mass. On imaging, they can be usually diagnosed with CT or MRI, due to presence of fat cells in the mass (Jinzaki et al, 2014). Renal angiomyolipomas may extend to perirenal or renal sinus fat and involve regional lymphatics and other visceral organs (Minja et al, 2012). The presence of renal angiomyolipomas in extrarenal sites is a manifestation of multicentricity rather than metastatic potential, and malignant angiomyolipomas are exceedingly rare (Zhan et al, 2018).

Angiomyolipomas are found in approximately 45–80% of patients with tuberous sclerosis and are typically bilateral and asymptomatic (Aydin et al, 2009). Tuberous sclerosis is a familial inherited disorder comprising adenoma sebaceum, mental retardation, and epilepsy (Nickerson et al, 2002). In patients without tuberous sclerosis, renal angiomyolipomas can be unilateral and tend to be larger than those associated with tuberous sclerosis.

The diagnosis of renal angiomyolipoma has evolved with the widespread use of US and CT. Ultrasonography and CT are frequently diagnostic in lesions with high fat content. Fat visualized on US appears as ultra-high-intensity echoes. Fat imaged by CT has a negative density, −20 to −80 Hounsfield units, which is pathognomonic for angiomyolipomas when observed in the kidney (Figure 20–2) (Jinzaki et al, 2014). MRI can also be utilized to identify fat within the lesion and confirm a diagnosis of angiomyolipoma. MRI is particularly useful in distinguishing lipid-poor angiomyolipomas, which have much lower fat content compared to routine angiomyolipomas, from other solid renal lesions (Kim et al, 2006).

The management of angiomyolipomas historically has been correlated with symptoms. In a long term study of patients with angiomyolipoma, patinets were divided into those with masses smaller or larger than 4 cm (Steiner et al, 1993).

The authors proposed that patients with isolated lesions <4 cm be followed up with yearly CT or US. Patients with asymptomatic or mildly symptomatic lesions >4 cm should be followed up with semiannual US. Patients with lesions >4 cm with moderate or severe symptoms (bleeding or pain) should undergo kidney-sparing surgery or renal arterial embolization. Recent data indicate that even larger angiomyolipomas (AMLs), measuring ≤ 8 cm, can be observed and treated as dictated by symptoms. Approximately 25–30% of patients who are observed will ultimately require treatment in the form of embolization, surgery, or radiofrequency ablation (Sooriakumaran et al, 2009). Immunosuppressiveagents such as sirolimus (an inhibitor of mammalian target of rapamycin or mTOR) may also be effective in treating AML arising in patients with tuberous sclerosis or those with multifocal AMLs (Bissler et al, 2008).

Other Rare Benign Renal Tumors

Several other benign renal tumors are quite rare, including leiomyomas, hemangiomas, lipomas, and juxtaglomerular cell tumors. With the exception of juxtaglomerular tumors, there are no features that unequivocally establish the diagnosis before surgery; therefore, the pathologist most often provides the diagnosis after resection.

Leiomyomas are rare small tumors typically found in smooth-muscle-containing areas of the kidney, including the renal capsule and renal pelvis. On imaging, they have regular outer margins, are hypoechoic on US, and slightly hyperdense on noncontrast CT and hypodense after contrast administration (Derchi et al, 2008). They are generally small and noted after surgical resection. If diagnosed on biopsy, they can be managed conservatively with observation (Romero et al, 2005).

Hemangiomas are small vascular tumors occurring in the kidney with a frequency second only to that in the liver among visceral organs. Multiple lesions in one kidney occur in approximately 12% of cases; however, they are rarely bilateral. They can occasionally be the elusive source of hematuria in an otherwise well-evaluated patient. The diagnosis may be determined by CT angiography, MR angiography, or by direct visualization by endoscopy (Lee et al, 2000). If symptomatic, they can often be managed by endoscopic fulgration or laser ablation (Daneshmand and Huffman, 2002).

Renal lipomas are very uncommon deposits of mature adipose cells without evident mitosis that arise from the renal capsule or perirenal tissue. They are seen primarily in middle-aged females and, owing to the characteristic CT differentiation of fat, are best detected radiographically on CT scanning.

Papillary adenomas are often incidentally identified in nephrectomy specimens, found more often in kidneys harboring papillary renal call carcinoma than clear cell carcinoma. They are immunohistochemically similar to papillary renal cell carcinoma and may represent a continuum of disease (Wang et al, 2007).

The **juxtaglomerular cell tumor** is the most clinically significant member of this subgroup of rare benign tumors because it causes significant hypertension that can be cured by surgical treatment. It is a very rare lesion, with <100 reported cases, and may have characteristic chromosomal alterations (Brandal et al, 2005). The tumors occur more commonly in young adults, more often in females in their 20s and 30s, and are rarely malignant. The tumors originate from the pericytes of afferent arterioles in the juxtaglomerular apparatus and can be shown to contain renin secretory granules. They are typically encapsulated and located in the cortical area. Symptoms of the "typical" tumors include hypertension, hypokalemia, hyperaldosteronism, and high renin content (Dong et al, 2010). Some atypical cases may demonstrate just hypertension with normal potassium levels or may even be nonfunctional. The diagnosis is confirmed by selected renal vein sampling for renin. Although complete nephrectomy was advocated in the past, several reports indicate that partial nephrectomy can be equally effective (Haab et al, 1995).

WILMS TUMOR (NEPHROBLASTOMA)

Nephroblastoma, also known as **Wilms tumor**, is the most common solid renal tumor of childhood, accounting for roughly 5% of childhood cancers. Approximately 650 new cases are reported annually. The peak age for presentation is during the third year of life, and there is no sex predilection. The disease is seen worldwide with a similar age of onset and sex distribution. Tumors are commonly unicentric, but they occur in either kidney with equal frequency. In 5% of cases the tumors are bilateral.

Wilms tumor occurs in familial and nonfamilial forms. The National Wilms Tumor Study (NWTS) group documented the occurrence of a familial Wilms tumor in approximately 1% of cases (Breslow and Beckwith, 1982). Although a relatively rare neoplasm, Wilms tumor has become a very important model for the study of tumorigenesis and has become a prototypical neoplasm for collaborative clinical trials, with approximately 85% of all new cases diagnosed in North America enrolled in NWTS group protocols (Beckwith, 1997). Approximately 10% of patients with Wilms tumors have recognized congenital malformations. Among the more common disorders associated with Wilms tumor are the WAGR syndrome (Wilms, aniridia, genitourinary malformation, mental retardation), overgrowth syndromes, such as the Beckwith–Wiedemann syndrome and isolated hemihypertrophy, and nonovergrowth disorders, such as isolated aniridia and trisomy 18 (Wiener et al, 1998). Genitourinary abnormalities such as hypospadias, cryptorchidism, and renal fusion are found in 4.5–7.5% of patients with unilateral Wilms tumor and in up to 13.4% of those with bilateral disease (Breslow et al, 1993). Some of these genetic syndromes are associated with alterations in the WT1 gene, but other genes such as the IGF1, H19, and p57 genes can also be implicated (Beckwith–Wiedemann).

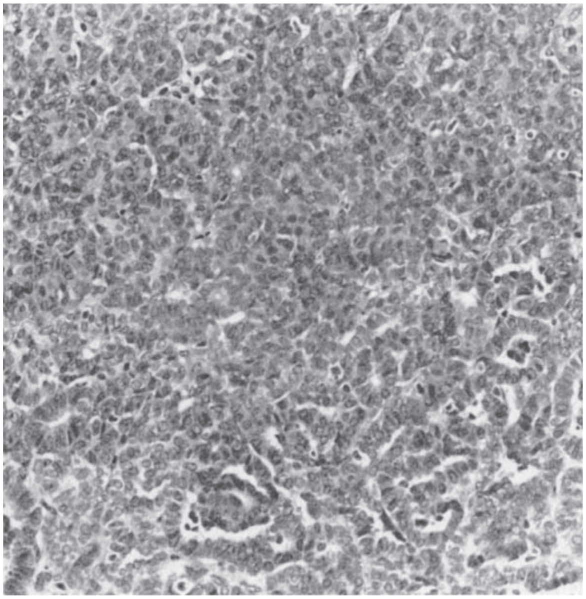
Etiology

In 1972 Knudson and Strong proposed a two-hit hypothesis to explain the earlier age of onset and bilateral presentation in children with a familial history of Wilms tumor. In this hypothesis, the pathogenesis of the sporadic form of Wilms tumor results from two postzygotic mutations in a single cell. In contrast, the familial form of the disease arises after one prezygotic mutation and a subsequent postzygotic event. Karyotypic analyses of Wilms tumor patients with various congenital malformations and loss of heterozygosity studies helped identify a region on the short arm of chromosome 11 (11p13) (Riccardi et al, 1978). This work ultimately led to the identification of a gene associated with Wilms tumor development (WT1), which maps to chromosome 11p13 (Epstein et al, 1994). Although alterations in this gene have been associated with Wilms tumor and genitourinary abnormalities, only 5–10% of sporadic Wilms tumors have been demonstrated to have WT1 mutations (Varanasi et al, 1994).

Pathogenesis and Pathology

In 1990 Beckwith and colleagues proposed a simplified nomenclature and classification of Wilms tumor precursor lesions known as **nephrogenic rests (NRs)**. Two distinct categories of NR were identified and designated as perilobar NR and intralobar NR. One concept of Wilms tumor development proposed that some NR remain dormant for many years, with some undergoing involution and sclerosis and others giving rise to Wilms tumors (Beckwith, 1997; Beckwith et al, 1990). The typical Wilms tumor consists of blastemal, epithelial, and stromal elements in varying proportions (Figure 20–10). Tumors composed of blastema and stroma or blastema alone have been described. Pure tubular and papillary forms that are very similar to papillary RCC have also been described.

The NWTS correlated pathologic specimens with clinical outcome and divided various histologic features into favorable and unfavorable prognostic groups. The unfavorable subgroup includes tumors that contain focal or diffuse elements of anaplastic cells or two other neoplastic entities considered not to be Wilms tumor variants, clear cell sarcoma of the kidney, and rhabdoid tumor of the kidney (Beckwith, 1997; Beckith and Palmer, 1978). Favorable histology tumors include all Wilms tumors without anaplasia. Anaplastic tumors are characterized by extreme nuclear atypia, hyperdiploidy, and numerous complex translocations. Anaplasia occurs in 5% of Wilms tumors and incidence increases with age. It is more common in African-American children and is linked to p53 mutations (Bardeesy et al, 1994). The presence of diffuse anaplasia indicates a worse prognosis compared to focal anaplasia.



▲ **Figure 20–10.** Wilms tumor with characteristic tubular/glomeruloid structures and blastema (original magnification ×40).

Grossly, Wilms tumors are generally large, multilobulated, and gray or tan in color with focal areas of hemorrhage and necrosis. A fibrous pseudocapsule is occasionally seen. Tumor dissemination can occur by direct extension through the renal capsule, hematogenously via the renal vein and vena cava, or via lymphatic spread. Metastatic disease is present at diagnosis in 10–15% of patients, with the lungs (85–95%) and liver (10–15%) the most common sites of involvement. Regional lymphatics are involved in as many as 25% of patients. Metastases to liver, bone, and brain are uncommon.

Tumor Staging

The NWTS staging system is most widely used and is based on surgical and pathologic findings. The original classification was used in the first and second NWTS trials and was modified for NWTS III (D'Angio et al, 1989). Further modifications have been introduced to the staging in the NWTS V study.

Stage I—Tumor limited to kidney and completely excised. No penetration of renal capsule or involvement of renal sinus vessels. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of resection.

Stage II—Tumor extends beyond the kidney but is completely removed. There is either penetration through the outer surface of the renal capsule, invasion of renal sinus vessels, biopsy of tumor before removal, or spillage of tumor locally during removal. There is no residual tumor apparent at or beyond the margins of excision and no lymph node involvement.

Stage III—Residual nonhematogenous tumor confined to abdomen. Any one or more of the following occur: (a) regional lymph node involvement; (b) diffuse peritoneal contamination by tumor, such as spillage of tumor beyond the flank before or during surgery, or by tumor growth that has penetrated through the peritoneal surface; (c) implants found on the peritoneal surfaces; (d) tumor extending beyond the surgical margins either microscopically or grossly; (e) tumor not completely resectable because of local infiltration into vital structures; (f) tumor spill not confined to the flank occurring either before or during surgery; and/or (g) transected tumor thrombus.

Stage IV—Hematogenous metastases to lung, liver, bone, and brain.

Stage V—Bilateral renal involvement at diagnosis. An attempt should be made to stage each side according to the previously given criteria according to the extent of disease before biopsy.

Clinical Findings

A. Symptoms and Signs

The diagnosis of Wilms tumor is most commonly made after the discovery of an asymptomatic mass by a family member or a physician during a routine physical examination. Common symptoms at presentation include abdominal pain and distention, anorexia, nausea and vomiting, fever, and hematuria. The most common sign is an abdominal mass. Hypertension is seen in 25–60% of cases and is caused by elevated renin levels (Pizzo et al, 2016). Up to 30% of patients demonstrate hematuria and coagulopathy can occur in 10%.

B. Laboratory Analysis

Urinalysis may show evidence of hematuria, and anemia may be present, particularly in patients with evidence of subcapsular hemorrhage. Patients with liver metastases may have abnormal serum chemistries.

C. Imaging

Abdominal US and CT scanning are performed initially to evaluate the mass. CT of the abdomen is performed with suspected Wilms tumor and can be useful in providing information regarding tumor extension, the status of the contralateral kidney, and the presence of regional adenopathy. CT scanning remains an imperfect technique with a relatively high false-positive rate for hepatic invasion in right-sided tumors, and 7% of cases of surgically confirmed synchronous bilateral Wilms tumors were missed by preoperative CT imaging in the NWTS IV (Ritchey et al, 1995).

Abdominal MRI can sometimes be useful to distinguish between NR and Wilms tumor but is otherwise not routinely indicated. MRI can also provide important information in defining the extent of tumor into the inferior vena cava, including those with intracardiac extension. MRI is limited in that there is no bowel contrast agent, and its use in children requires sedation.

Chest x-ray remains the initial examination of choice to evaluate for the presence of lung metastases. The role of a chest CT scan is controversial, and it is probably not indicated for routine use in low-risk patients; however, when done concomitantly with an abdominal CT, chest CT may provide clinically useful information in high-risk patients. If pulmonary metastases are seen on chest x-ray, CT of the chest will not alter current therapy. However, the need for chest CT imaging in patients with negative results of chest x-ray remains controversial, because it is not clear whether those lesions detected by CT alone require more aggressive treatment.

D. Needle Biopsy

Preoperative biopsy is indicated routinely only in tumors deemed too large for safe primary surgical resection and for which preoperative chemotherapy or radiation therapy is planned.

Differential Diagnosis

The differential diagnosis of a flank mass in a child includes hydronephrosis, cystic kidneys, intrarenal neuroblastoma, mesoblastic nephroma, and various very rare sarcomas.

Ultrasonography can confirm the presence of hydronephrosis and evaluate for the presence of cystic kidneys. Neuroblastoma, while pathologically distinct from Wilms tumor, frequently presents in the abdomen as a mass arising from the adrenal glands or paraspinal ganglion. Neuroblastomas are radiographically indistinguishable from Wilms tumors, but there are several features that may aid in the differentiation. In contrast to Wilms tumors, which are typically confined to one side of the abdomen, neuroblastomas usually cross the midline. Wilms tumors are intrarenal masses and rarely cause a change in the axis of the kidney, while neuroblastomas may cause an outward and downward displacement of the kidney ("drooping lily"). Children with neuroblastomas are more likely to present with metastatic disease, and these tumors have a higher frequency of calcification observed radiographically. In addition, neuroblastomas may produce various tumor markers including vanillylmandelic acid and other catecholamines that are not seen in patients with Wilms tumor.

Mesoblastic nephromas are benign hamartomas and cannot be preoperatively distinguished from Wilms tumors. They are most commonly seen in the neonatal period and are typically identified by surgical pathology after nephrectomy. The tumor can occur in adults.

Treatment

The goal of therapy is to provide the highest possible cure rate with the lowest treatment-related morbidity. Significant improvements in survival rates for children with Wilms tumor have been achieved by an improved understanding of the disease and a multimodality approach to therapy, advocated by the National Wilms Tumor Registry (NWTS), which incorporates surgery, radiation therapy, and chemotherapy.

A. Surgical Measures

For patients with unilateral kidney involvement whose tumors are deemed surgically resectable (tumors not crossing the midline or involving adjacent visceral organs), radical nephrectomy via a transabdominal incision is the procedure of choice.

Retroperitoneal lymph node dissection is not of proven value and is not recommended. However, biopsy of regional lymphatics (renal hilum and para-aortic nodes) and careful examination of the opposite kidney and the remainder of the abdomen provide crucial data for staging and prognosis. Tumor extending into the vena cava should be removed unless there is evidence of total obstruction. Excision of tumor extending into adjacent organs can be attempted if feasible. Complete excision of all tumors would allow downstaging and decrease the amount of additional chemotherapy. A major point of emphasis during surgical extirpation is to avoid spillage because there is evidence that this increases abdominal recurrence of disease (Ross and Kay, 1999; Shamberger et al, 171).

A child with bilateral Wilms tumor, like an adult with bilateral RCC, requires an individualized approach. Patients with favorable histology tumors can frequently be managed with preoperative chemotherapy followed by renal-sparing surgery (Kumar et al, 1998). In patients for whom preoperative chemotherapy is planned, a biopsy for diagnosis and staging is indicated (Blute et al, 1987; Charlton et al, 2017). In some centers, needle aspiration biopsy has proved to be a reliable diagnostic tool when evaluated by experienced pathologists. In patients with unfavorable histology tumors, the therapeutic approach consists of aggressive surgery followed by chemotherapy and radiation therapy.

B. Chemotherapy

Wilms tumor has been long recognized as a chemosensitive neoplasm. Consecutive multicenter randomized trials conducted by the National Wilms' Tumor Study Group (NWTSG), starting in the 1960s, have carefully explored various treatment strategies to determine the role of various antineoplastics and the integration of surgery and radiotherapy, with the goal of optimizing response rates and cure while minimizing the toxicity of therapy. Current studies are focused on continued efforts to minimize toxicity (primarily by decreasing chemotherapy treatment duration and removing radiotherapy) in those favorable subgroups with impressive cure rates and modifying efforts in poor-risk subgroups to improve response and survival.

Patients with stage I favorable or anaplastic histology and stage II favorable histology tumors undergo surgical resection and have adjuvant chemotherapy with vincristine and dactinomycin combinations without radiotherapy. Patients with stages III and IV favorable histology tumors undergo surgical resection and have adjuvant therapy with vincristine, dactinomycin, and doxorubicin, with adjuvant radiotherapy. Patients with stages II–IV focally anaplastic histology tumors receive therapy similar to that for advanced-stage favorable histology tumors. In the NWTS V, patients with stages II–IV anaplastic tumors are receiving vincristine, doxorubicin, cyclophosphamide, and etoposide (Kalapurakal et al, 2004). Salvage chemotherapy regimens include agents such as cyclophosphamide, ifosfamide, carboplatin, and etoposide. For stage V or bilateral Wilms tumors, diagnosis is established by bilateral biopsies followed by chemotherapy. Second-look surgery may be necessary to reassess response 6–8 weeks after chemotherapy. Renal sparing procedures can be attempted but the rate of renal failure is high.

C. Radiation Therapy

Wilms tumor has long been recognized as a radiosensitive tumor. Despite the proven efficacy of radiation therapy in children, its use is complicated by its potential for growth disturbances and recognized cardiac, pulmonary, and hepatic toxicities. The development of effective chemotherapy combinations has practically replaced radiation therapy in the preoperative setting. The first and second NWTS trials demonstrated that postoperative radiotherapy was not required for patients with favorable histology stage I disease. NWTS III failed to show an advantage for postoperative radiotherapy in patients with favorable stage II disease and demonstrated that the relapse rate of patients with stage III disease was no different for patients receiving 1000 cGy compared with the traditional 2000 cGy (D'Angio et al, 1989). Postoperative radiation is recommended for patients with stage III or IV disease with favorable histology, stages II–IV with focal anaplasia and clear cell sarcoma, and all stages of rhabdoid tumor of the kidney.

Prognosis

The multimodality approach to the treatment of children with Wilms tumors has significantly improved outcomes. The 4-year survival of patients with favorable histology Wilms tumor now approaches 90% (Aldrink et al, 2018). The most important negative prognostic factors remain the unfavorable histologic subtypes (clear cell sarcoma, rhabdoid, and anaplastic tumors). Although the addition of doxorubicin in NWTS III significantly improved the 2-year survival rate for patients with clear cell sarcomas (62–91%), it did not affect the survival of children with rhabdoid tumors. Analysis of patients with bilateral Wilms tumors registered with

NWTS II and III revealed a 3-year survival rate of 82% (Blute et al, 1987; Charlton et al, 2017).

Future challenges include improvements in therapy for patients with anaplastic tumors (stages II–IV), clear cell sarcoma, and rhabdoid tumors, and efforts to improve outcomes in favorable histology tumors while decreasing both short-term and late toxicities. Long-term toxicity in these patients include renal failure, cardiac toxicity with congestive heart failure due to chemotherapy, and lung radiation as well as a higher risk for secondary malignancies.

SECONDARY RENAL TUMORS

The kidney is a frequent site for metastatic spread of both solid and hematologic tumors. In a survey of 4413 autopsies at a major cancer center, there were 81 (1.8%) cases of secondary carcinoma of the kidney (hematologic tumors were excluded) (Wagle et al, 1975). The most frequent primary site of cancer was the lung (20%), followed by the breast (12%), the stomach (11%), and the kidneys (9%). The authors noted that metastases to the renal parenchyma typically demonstrated capsular and stromal invasion with sparing of the renal pelvis, and that bilateral secondary renal involvement was found in approximately 50% of cases. Secondary metastatic disease to the kidneys tends to be a late event, frequently in the setting of widely disseminated disease, which typically portends a poor prognosis. Therapy is dictated by the responsiveness of the primary neoplasm; that is, patients with breast and ovarian cancers for which there is effective therapy are more likely to respond than patients with primary lung or gastric cancers.

Autopsy series have reported clinically evident renal invasion by lymphoma to be 0.5–7%, with the rates of Hodgkin's and non-Hodgkin's lymphoma distributed equally (Weimar et al, 1981). Renal involvement is usually in the form of bilateral, multiple, discrete tumor nodules. Renal involvement by non-Hodgkin's lymphoma is typically characterized by diffuse, aggressive histologic findings (ie, diffuse large cell) in the setting of extensive disease. Therapy typically consists of combination chemotherapy, with the prognosis of patients similar to that of patients without renal involvement but with widely disseminated, aggressive lymphomas.

BIBLIOGRAPHY

Adamy A, Lowrance WT, Yee DS, et al: Renal oncocytosis: Management and clinical outcomes. J Urol 2011;185:795–801.

Aldrink JH, Heaton TE, Dasgupta R, et al: Update on Wilms tumor. J Pediatr Surg 2018. (Available online at: https://linkinghub.elsevier.com/retrieve/pii/S002234681830575X; accessed 1/20/19.)

Amin MB, American Joint Committee on Cancer and American Cancer Society (eds): AJCC Cancer Staging Manual. 8th ed. American Joint Committee on Cancer, Springer, Chicago, 2017.

Anonymous: The European Chromosome 16 Tuberous Sclerosis Consortium: Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 1993;75:1305–1315.

Aslam Sohaib S, Teh J, Nargund VH, et al: Assessment of tumor invasion of the vena caval wall in renal cell carcinoma cases by magnetic resonance imaging. J Urol 2002;167:1271–1275.

Aydin H, Magi-Galluzzi C, Lane BR, et al: Renal angiomyolipoma: Clinicopathologic study of 194 cases with emphasis on the epithelioid histology and tuberous sclerosis association. Am J Surg Pathol 2009;33.

Badalato GM, Kates M, Wisnivesky JP, et al: Survival after partial and radical nephrectomy for the treatment of stage T1bN0M0 renal cell carcinoma (RCC) in the USA: A propensity scoring approach: Survival after PN and RN for stage T1bN0M0 RCC in the USA. BJU Int 2012;109:1457–1462.

Bardeesy N, Falkoff D, Petruzzi M-J, et al: Anaplastic Wilms' tumour, a subtype displaying poor prognosis, harbours p53 gene mutations. Nat Genet 1994;7:91.

Beckwith JB, Kiviat NB, Bonadio JF: Nephrogenic rests, nephroblastomatosis, and the pathogenesis of Wilms' tumor. Pediatr Pathol 1990;10:1–36.

Beckwith JB, Palmer NF: Histopathology and prognosis of Wilms tumorResults from the first national wilms' tumor study. Cancer 1978;41:1937–1948.

Beckwith JB: New developments in the pathology of Wilms tumor: Pediatric oncology. Cancer Invest 1997;15:153–162.

Bertolotto M, Bucci S, Valentino M, et al: Contrast-enhanced ultrasound for characterizing renal masses. Eur J Radiol 2018;105: 41–48.

Bissler JJ, Christopher Kingswood J: Renal manifestation of tuberous sclerosis complex. Am J Med Genet C Semin Med Genet 2018; 178:338–347.

Bissler JJ, McCormack FX, Young LR, et al: Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. New Engl J Med 2008;358:140–151.

Blom JHM, van Poppel H, Maréchal JM, et al: Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol 2009;55:28–34.

Blute ML, Kelalis PP, Offord KP, et al: Bilateral Wilms tumor. J Urol 1987;138:968–973.

Bosniak MA: The current radiological approach to renal cysts. Radiology 1986;158:1–10.

Brandal P, Busund L-T, Heim S: Chromosome abnormalities in juxtaglomerular cell tumors. Cancer 2005;104:504–510.

Brennan JF, Stilmant MM, Babayan RK, et al: Acquired renal cystic disease: Implications for the urologist. Br J Urol 2018;67: 342–348.

Breslow N, Olshan A, Beckwith JB, et al: Epidemiology of Wilms tumor. Med Pediatr Oncol 1993;21:172–181.

Breslow NE, Beckwith JB: Epidemiological features of Wilms' tumor: Results of the National Wilms' Tumor Study 2. J Natl Cancer Inst 1982;68:429–436.

Campbell S, Uzzo RG, Allaf ME, et al: Renal mass and localized renal cancer: AUA guideline. J Urol 2017;198:520–529.

Charlton J, Irtan S, Bergeron C, et al: Bilateral Wilms tumour: A review of clinical and molecular features. Expert Rev Mol Med 2017;19. (Available online at: https://www.cambridge.org/core/product/identifier/S1462399417000084/type/journal_article; accessed 1/20/19.)

Chen F, Kishida T, Yao M, et al: Germline mutations in the von Hippel–Lindau disease tumor suppressor gene: Correlations with phenotype. Hum Mutat 1995;5:66–75.

Choueiri TK, Halabi S, Sanford BL, et al: Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The alliance A031203 CABOSUN trial. J Clin Oncol 2017;35:591–597.

Crépel M, Jeldres C, Perrotte P, et al: Nephron-sparing surgery is equally effective to radical nephrectomy for T1BN0M0 renal cell carcinoma: A population-based assessment. Urology 2010;75: 271–275.

Dabestani S, Thorstenson A, Lindblad P, et al: Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: A population-based study. World J Urol 2016;34:1081–1086.

Daneshmand S, Huffman JL: Endoscopic management of renal hemangioma. J Urol 2002;167:488–489.

D'Angio GJ, Breslow N, Beckwith JB, et al: Treatment of Wilms' tumor. Results of the third national Wilms' tumor study. Cancer 1989;64:349–360.

Delahunt B, Cheville JC, Martignoni G, et al: The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 2013;37:1490–1504.

Derchi LE, Grenier N, Heinz-Peer G, et al: Imaging of renal leiomyomas. Acta Radiol 2008;49:833–838.

DiBiase SJ, Valicenti RK, Schultz D, et al: Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: Support for dose escalation based on a biological model. J Urol 1997; 158:746–749.

Ding G-X, Feng C-C, Song N-H, et al: Paraneoplastic symptoms: Cachexia, polycythemia, and hypercalcemia are, respectively, related to vascular endothelial growth factor (VEGF) expression in renal clear cell carcinoma. Urol Oncol 2013;31(8): 1820–1825.

Donat SM, Diaz M, Bishoff JT, et al: Follow-up for clinically localized renal neoplasms: AUA guideline. J Urol 2013;190:407–416.

Dong D, Li H, Yan W, et al: Juxtaglomerular cell tumor of the kidney—a new classification scheme. Urol Oncol Semin Orig Invest 2010; 28:34–38.

Duchene DA, Lotan Y, Cadeddu JA, et al: Histopathology of surgically managed renal tumors: Analysis of a contemporary series. Urology 2003;62:827–830.

Elahmadawy MA, Elazab MSS, Ahmed S, et al: Diagnostic value of F-18 FDG PET/CT for local and distant disease relapse surveillance in surgically treated RCC patients: Can it aid in establishing consensus follow up strategy? Nucl Med Rev 2018;21:85–91.

Epstein FH, Coppes MJ, Haber DA, et al: Genetic events in the development of Wilms' tumor. New Engl J Med 1994;331:586–590.

Escudier B, Bellmunt J, Negrier S, et al: Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): Final analysis of overall survival. J Clin Oncol 2010;28:2144–2150.

Ficarra V, Novara G, Secco S, et al: Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nephron-sparing surgery. Eur Urol 2009;56:786–793.

Flanigan RC, Mickisch G, Sylvester R, et al: Cytoreductive nephrectomy in patients with metastatic renal cancer: A combined analysis. J Urol 2004;171:1071–1076.

Flanigan RC, Salmon SE, Blumenstein BA, et al: Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. New Engl J Med 2001;345: 1655–1659.

Fuhrman SA, Lasky LC, Limas C: Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655–663.

Fyfe G, Fisher RI, Rosenberg SA, et al: Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol Off J Am Soc Clin Oncol 1995;13:688–696.

Gansler T, Fedewa S, Amin MB, et al: Trends in reporting histological subtyping of renal cell carcinoma: Association with cancer center type. Hum Pathol 2018;74:99–108.

Gershman B, Thompson RH, Boorjian SA, et al: Radical versus partial nephrectomy for cT1 renal cell carcinoma. Eur Urol 2018; 74:825–832.

Giunchi F, Fiorentino M, Vagnoni V, et al: Renal oncocytosis: A clinicopathological and cytogenetic study of 42 tumours occurring in 11 patients. Pathology (Philadelphia) 2016;48: 41–46.

Gold PJ, Fefer A, Thompson JA: Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol 1996;14:216–222.

Goldner W: Cancer-related hypercalcemia. J Oncol Pract 2016;12: 426–432.

Gorin MA, Rowe SP, Baras AS, et al: Prospective evaluation of 99mTc-sestamibi SPECT/CT for the diagnosis of renal oncocytomas and hybrid oncocytic/chromophobe tumors. Eur Urol 2016;69:413–416.

Gorin MA, Rowe SP, Hooper JE, et al: PSMA-targeted18F-DCFPyL PET/CT imaging of clear cell renal cell carcinoma: Results from a rapid autopsy. Eur Urol 2017;71:145–146.

Graham J, Dudani S, Heng DYC: Prognostication in kidney cancer: Recent advances and future directions. J Clin Oncol 2018;36: 3567–3573.

Gross-Goupil M, Kwon TG, Eto M, et al: Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Ann Oncol 2018;29:2371–2378.

Gulanikar AC, Daily PP, Kilambi NK, et al: Prospective pretransplant ultrasound screening in 206 patients for acquired renal, cysts and renal, cell carcinoma. Transplantation 1998;66:1669–1672.

Haab F, Duclos JM, Guyenne T, et al: Renin secreting tumors: Diagnosis, conservative surgical approach and long-term results. J Urol 1995;153:1781–1784.

Haas NB, Manola J, Uzzo RG, et al: Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387:2008–2016.

Hansen J, Sun M, Bianchi M, et al: Assessment of cancer control outcomes in patients with high-risk renal cell carcinoma treated with partial nephrectomy. Urology 2012;80:347–353.

Hegemann M, Kroeger N, Stenzl A, et al: Rare and changeable as a chameleon: Paraneoplastic syndromes in renal cell carcinoma. World J Urol 2018;36:849–854.

Heng DYC, Xie W, Regan MM, et al: External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013;14:141–148.

Heng DYC, Xie W, Regan MM, et al: Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 2009;27(43):5794–5799.

Henriksson C, Haraldsson G, Aldenborg F, et al: Skeletal metastases in 102 patients evaluated before surgery for renal cell carcinoma. Scand J Urol Nephrol 1992;26:363–366.

Herts BR, Silverman SG, Hindman NM, et al: Management of the incidental renal mass on CT: A white paper of the ACR Incidental Findings Committee. J Am Coll Radiol 2018;15:264–273.

Hudes G, Carducci M, Tomczak P, et al: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. New Engl J Med 2007;356:2271–2281.

Hunt JD, van der Hel OL, McMillan GP, et al: Renal cell carcinoma in relation to cigarette smoking: Meta-analysis of 24 studies. Int J Cancer 2005;114:101–108.

Israel GM, Bosniak MA: An update of the Bosniak renal cyst classification system. Urology 2005;66:484–488.

Jinzaki M, Silverman SG, Akita H, et al: Renal angiomyolipoma: A radiological classification and update on recent developments in diagnosis and management. Abdom Imag 2014;39:588–604.

Joniau S, Eeckt KV, Srirangam SJ, et al: Outcome of nephron-sparing surgery for T1b renal cell carcinoma. BJU Int 2009;103:1344–1348.

Kalapurakal JA, Dome JS, Perlman EJ, et al: Management of Wilms' tumour: current practice and future goals. Lancet Oncol 2004;5:37–46.

Karakiewicz PI, Hutterer GC, Trinh Q-D, et al: C-reactive protein is an informative predictor of renal cell carcinoma-specific mortality. Cancer 2007;110:1241–1247.

Kim HL, Belldegrun AS, Freitas DG, et al: Paraneoplastic signs and symptoms of renal cell carcinoma: Implications for prognosis. J Urol 2003;170:1742–1746.

Kim JK, Kim SH, Jang YJ, et al: Renal angiomyolipoma with minimal fat: Differentiation from other neoplasms at double-echo chemical shift FLASH MR imaging. Radiology 2006;239:174–180.

Kopp RP, Mehrazin R, Palazzi KL, et al: Survival outcomes after radical and partial nephrectomy for clinical T2 renal tumours categorised by R.E.N.A.L. nephrometry score: Radical vs partial nephrectomy for T2 renal mass. BJU Int 2014;114:708–718.

Kumar R, Fitzgerald R, Breatnach F: Conservative surgical management of bilateral Wilms tumor: Results of the United Kingdom Children's Cancer Study Group. J Urol 1998;160:1450–1453.

Kutikov A, Uzzo RG: The R.E.N.A.L. nephrometry score: A comprehensive standardized system for quantitating renal tumor Size, location and depth. J Urol 2009;182:844–853.

La Vecchia C, Negri E, Avanzo B, et al: Smoking and renal cell carcinoma. Cancer Res 1990;50:5231–5233.

Lane BR, Campbell SC, Demirjian S, et al: Surgically induced chronic kidney disease may mbe associated with a lower risk of progression and mortality than medical chronic kidney disease. J Urol 2013;189:1649–1655.

Lang M, Vocke CD, Merino MJ, et al: Mitochondrial DNA mutations distinguish bilateral multifocal renal oncocytomas from familial Birt–Hogg–Dubé tumors. Mod Pathol 2015;28:1458.

Latif F, Tory K, Gnarra J, et al: Identification of the von Hippel-Lindau disease tumor suppressor gene. Science 1993;260:1317–1320.

Lee H-S, Koh B-H, Kim J-W, et al: Radiologic findings of renal hemangioma: Report of three cases. Korean J Radiol 2000;1:60–63.

Leibovich BC, Blute ML, Cheville JC, et al: Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. J Urol 2004;171:1066–1070.

Leibovich BC, Blute ML: Lymph node dissection in the management of renal cell carcinoma. Urol Clin North Am 2008;35:673–678.

Leveridge MJ, Bostrom PJ, Koulouris G, et al: Imaging renal cell carcinoma with ultrasonography, CT and MRI. Nat Rev Urol 2010;7:311–325.

Linehan WM, Ricketts CJ: The metabolic basis of kidney cancer. Semin Cancer Biol 2013;23:46–55.

Lobo JM, Nelson M, Nandanan N, et al: Comparison of renal cell carcinoma surveillance guidelines: Competing trade-offs. J Urol 2016;195:1664–1670.

Long CJ, Canter DJ, Kutikov A, et al: Partial nephrectomy for renal masses ≥7 cm: Technical, oncological and functional outcomes: PN for renal masses ≥7 cm. BJU Int 2012;109:1450–1456.

Lotan Y, Karam JA, Shariat SF, et al: Renal-cell carcinoma risk estimates based on participants in the prostate, lung, colorectal, and ovarian cancer screening trial and national lung screening trial. Urol Oncol Semin Orig Invest 2016;34:167.e9.

Méjean A, Ravaud A, Thezenas S, et al: Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. New Engl J Med 2018;379:417–427.

Mackay B, Ordóñez NG, Khoursand J, et al: The ultrastructure and immunocytochemistry of renal cell carcinoma. Ultrastruct Pathol 1987;11:483–502.

Maddox M, Mandava S, Liu J, et al: Robotic partial nephrectomy for clinical stage T1b tumors: Intermediate oncologic and functional outcomes. Clin Genitourin Cancer 2015;13:94–99.

Mandel JS, McLaughlin JK, Schlehofer B, et al: International renal-cell cancer study. IV. Occupation. Int J Cancer 2018;61: 601–605.

McIntosh AG, Ristau BT, Ruth K, et al: Active surveillance for localized renal masses: Tumor growth, delayed intervention rates, and >5-yr clinical outcomes. Eur Urol 2018;74:157–164.

Meskawi M, Becker A, Bianchi M, et al: Partial and radical nephrectomy provide comparable long-term cancer control for T1b renal cell carcinoma: Partial nephrectomy in T1b RCC. Int J Urol 2014;21:122–128.

Mickisch GH, Garin A, van Poppel H, et al: Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial. Lancet 2001;358:966–970.

Minja EJ, Pellerin M, Saviano N, et al: Retroperitoneal extrarenal angiomyolipomas: An evidence-based approach to a rare clinical entity. Case Rep Nephrol 2012;2012:374107.

Mir MC, Derweesh I, Porpiglia F, et al: Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: A systematic review and meta-analysis of comparative studies. Eur Urol 2017;71:606–617.

Mir MC, Pavan N, Parekh DJ: Current paradigm for ischemia in kidney surgery. J Urol 2016;195:1655–1663.

Moch H, Humphrey PA, Ulbright TM, et al (eds): WHO Classification of Tumours of the Urinary System and Male Genital Organs. IARC Press, Lyon, France, 2016.

Motzer RJ, Bacik J, Murphy BA, et al: Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289–296.

Motzer RJ, Escudier B, Oudard S, et al: Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer 2010;116:4256–4265.

Motzer RJ, Haas NB, Donskov F, et al: Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol 2017;35:3916–3923.

Motzer RJ, Hutson TE, Cella D, et al: Pazopanib versus sunitinib in metastatic renal-cell carcinoma. New Engl J Med 2013;369:722–731.

Motzer RJ, Hutson TE, Tomczak P, et al: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27: 3584–3590.

Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New Engl J Med 2007;356:115–124.

Motzer RJ, Murphy BA, Bacik J, et al: Phase III trial of interferon alfa-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma. J Clin Oncol 2000;18:2972–2980.

Motzer RJ, Tannir NM, McDermott DF, et al: Nivolumab plus Ipilimum ab versus Sunitinib in advanced renal-cell carcinoma. New Engl J Med 2018:NEJMoa1712126.

Muglia VF, Westphalen AC: Bosniak classification for complex renal cysts: History and critical analysis. Radiol Bras 2014;47:368–373.

Nakanishi Y, Kitajima K, Yamada Y, et al: Diagnostic performance of 11C-choline PET/CT and FDG PET/CT for staging and restaging of renal cell cancer. Ann Nucl Med 2018;32(10):658–668.

Nickerson ML, Warren MB, Toro JR, et al: Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. Cancer Cell 2002;2:157–164.

Novara G, Ficarra V, Antonelli A, et al: Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: Are further improvements needed? Eur Urol 2010;58:588–595.

Novick AC, Stewart BH, Straffon RA: Extracorporeal renal surgery and autotransplantation: Indications, techniques and results. J Urol 1980;123:806–811.

Odisho AY, Etzioni R, Gore JL: Beyond classic risk adjustment: Socioeconomic status and hospital performance in urologic oncology surgery. Cancer 2018;124(16):3372–3380.

Onufrey V, Mohiuddin M: Radiation therapy in the treatment of me tastatic renal cell carcinoma. Int J Radiat Oncol 1985;11: 2007–2009.

Organ SL, Tsao M-S: An overview of the c-MET signaling pathway. Ther Adv Med Oncol 2011;3:S7–S19.

Paner GP, Stadler WM, Hansel DE, et al: Updates in the eighth edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. Eur Urol 2018;73:560–569.

Papworth K, Grankvist K, Ljungberg B, et al: Parathyroid hormone-related protein and serum calcium in patients with renal cell carcinoma. Tumour Biol J Int Soc Oncodev Biol Med 2005;26:201–206.

Pastore RD, Pfeffer LM, Nanus DM: Renal cell carcinoma and interferon at the millennium. Cancer Invest 2001;19:281–291.

Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of surgery in the treatment of single metastases to the brain. New Engl J Med 1990;322:494–500.

Patel HD, Johnson MH, Pierorazio PM, et al: Diagnostic accuracy and risks of biopsy in the diagnosis of a renal mass suspicious for localized renal cell carcinoma: Systematic review of the literature. J Urol 2016;195:1340–1347.

Pierorazio PM, Johnson MH, Patel HD, et al: Management of renal masses and localized renal cancer: Systematic review and meta-analysis. J Urol 2016;196:989–999.

Pizzo PA, Poplack DG, Adamson PC, et al: Principles and practice of pediatric oncology. Wolters Kluwer; 2016.

Ravaud A, Motzer RJ, Pandha HS, et al: Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. New Engl J Med 2016; 375:2246–2254.

Reichard EAP, Roubidoux MA, Dunnick NR: Renal neoplasms in patients with renal cystic diseases. Abdom Imaging 1998;23: 237.

Riccardi VM, Sujansky E, Smith AC, et al: Chromosomal imbalance in the Aniridia-Wilms' Tumor Association: 11p interstitial deletion. Pediatrics 1978;61:604.

Rini BI, Halabi S, Rosenberg JE, et al: Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: Final results of CALGB 90206. J Clin Oncol 2010;28:2137–2143.

Ritchey ML, Green DM, Breslow NB, et al: Accuracy of current imaging modalities in the diagnosis of synchronous bilateral Wilms' tumor. A report from the national wilms tumor study group. Cancer 1995;75:600–604.

Romero FR, Kohanim S, Lima G, et al: Leiomyomas of the kidney: Emphasis on conservative diagnosis and treatment. Urology 2005;66:1319.e1–1319.e3.

Romis L, Cindolo L, Patard JJ, et al: Frequency, clinical presentation and evolution of renal oncocytomas: Multicentric experience from a European database. Eur Urol 2004;45:53–57.

Ross JH, Kay R: Surgical considerations for patients with Wilms' tumor. Semin Urol Oncol 1999;17:33–39.

Rowe SP, Gorin MA, Hammers HJ, et al: Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted18F-DCFPyL PET/CT. Ann Nucl Med 2015;29:877–882.

Scelo G, Li P, Chanudet E, et al: Variability of sex disparities in cancer incidence over 30 years: The striking case of kidney cancer. Eur Urol Focus 2018;4:586–590.

Schmidt L, Duh F-M, Chen F, et al: Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 1997;16:68.

Shah PH, Moreira DM, Okhunov Z, et al: Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. J Urol 2016;196:327–334.

Shamberger RC, Guthrie KA, Ritchey ML, et al: Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg 1999;229:292–297.

Shin BJ, Chick JFB, Stavropoulos SW: Contemporary status of percutaneous ablation for the small renal mass. Curr Urol Rep 2016;17. (Available online at: http://link.springer.com/10.1007/s11934-016-0581-7; accessed 1/4/19.)

Shuch B, La Rochelle JC, Klatte T, et al: Brain metastasis from renal cell carcinoma: Presentation, recurrence, and survival. Cancer 2008;113:1641–1648.

Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. Cancer J Clin 2018;68:7–30.

Simhan J, Smaldone MC, Tsai KJ, et al: Perioperative outcomes of robotic and open partial nephrectomy for moderately and highly complex renal lesions. J Urol 2012;187:2000–2004.

Sinibaldi VJ, Pratz CF, Yankulina O: Kidney cancer: Toxicity management, symptom ontrol, and palliative care. J Clin Oncol 2018;36:3632–3638.

Siva S, Kothari G, Muacevic A, et al: Radiotherapy for renal cell carcinoma: Renaissance of an overlooked approach. Nat Rev Urol 2017;14:549.

Skinner DG ed: Urological Cancer. Grune & Stratton, New York, 1983.

Snyder ME, Bach A, Kattan MW, et al: Incidence of benign lesions for clinically localized renal masses smaller than 7 cm in radiological diameter: Influence of sex. J Urol 2006;176:2391–2396.

Sooriakumaran P, Gibbs P, Coughlin G, et al: Angiomyolipomata: Challenges, solutions, and future prospects based on over 100 cases treated. BJU Int 2009;105:101–106.

Speed JM, Trinh Q-D, Choueiri TK, et al: Recurrence in localized renal cell carcinoma: A systematic review of contemporary data. Curr Urol Rep 2017;18:15.

Stauffer M: Nephrogenic Hepatomegaly. In: Gastroenterology. Vol. 40. Elsevier, Chicago, 1961, pp. 665–697.

Steffens S, Köhler A, Rudolph R, et al: Validation of CRP as prognostic marker for renal cell carcinoma in a large series of patients. BMC Cancer 2012;12:399.

Steiner MS, Goldman SM, Fishman EK, et al: The natural history of renal angiomyolipoma. J Urol 1993;150:1782–1786.

Sternberg CN, Davis ID, Mardiak J, et al: Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. J Clin Oncol 2010;28:1061–1068.

Sternberg CN, Hawkins RE, Wagstaff J, et al: A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update. Eur J Cancer 2013;49:1287–1296.

Stewart-Merrill SB, Thompson RH, Boorjian SA, et al: Oncologic surveillance after surgical resection for renal cell carcinoma: A novel risk-based approach. J Clin Oncol 2015;33:4151–4157.

Sufrin G, Chasan S, Golio A, et al: Paraneoplastic and serologic syndromes of renal adenocarcinoma. Semin Urol 1989;7:158–171.

Tabayoyong W, Abouassaly R, Kiechle JE, et al: Variation in surgical margin status by surgical approach among patients undergoing partial nephrectomy for small renal masses. J Urol 2015;194:1548–1553.

Thoenes W, Störkel ST, Rumpelt H-J, et al: Chromophobe cell renal carcinoma and its variants—a report on 32 cases. J Pathol 2018;155:277–287.

Toro JR, Nickerson ML, Wei M-H, et al: Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 2003;73:95–106.

Torro JR, Glenn G, Duray P, et al: Birt-Hogg-Dubé syndrome: A novel marker of kidney neoplasia. Arch Dermatol 1999;135:1195–1202.

Uzosike AC, Patel HD, Alam R, et al: Growth kinetics of small renal masses on active surveillance: Variability and results from the DISSRM Registry. J Urol 2018;199:641–648.

Van Poppel H, Da Pozzo L, Albrecht W, et al: A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011;59:543–552.

Varanasi R, Bardeesy N, Ghahremani M, et al: Fine structure analysis of the WT1 gene in sporadic Wilms tumors. Proc Natl Acad Sci 1994;91:3554–3558.

Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al: Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery. Ann Neurol 1993;33:583–590.

Vogl UM, Zehetgruber H, Dominkus M, et al: Prognostic factors in metastatic renal cell carcinoma: Metastasectomy as independent prognostic variable. Br J Cancer 2006;95:691.

Wagle DG, Moore RH, Murphy GP: Secondary carcinomas of the kidney. J Urol 1975;114:30–32.

Wagner B, Patard J-J, Méjean A, et al: Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. Eur Urol 2009;55:452–459.

Wang CJ, Christie A, Lin M-H, et al: Safety and efficacy of stereotactic ablative radiation therapy for renal cell carcinoma extracranial metastases. Int J Radiat Oncol 2017;98:91–100.

Wang KL, Weinrach DM, Luan C, et al: Renal papillary adenoma—a putative precursor of papillary renal cell carcinoma. Hum Pathol 2007;38:239–246.

Wang ZJ, Westphalen AC, Zagoria RJ: CT and MRI of small renal masses. Br J Radiol 2018;91(1087):20180131.

Weimar G, Culp DA, Loening S, et al: Urogenital involvement by malignant lymphomas. J Urol 1981;125:230–231.

Whitson JM, Reese AC, Meng MV: Population based analysis of survival in patients with renal cell carcinoma and venous tumor thrombus. Urol Oncol 2013;31:259–263.

Wiener JS, Coppes MJ, Ritchey ML: Current concepts in the biology and management of Wilms tumor. J Urol 1998;159:1316–1325.

Wilkerson ML, Lin F, Liu H, et al: The application of immunohistochemical biomarkers in urologic surgical pathology. Arch Pathol Lab Med 2014;138:1643–1665.

Williamson SR, Gadde R, Trpkov K, et al: Diagnostic criteria for oncocytic renal neoplasms: A survey of urologic pathologists. Hum Pathol 2017;63:149–156.

Wobker SE, Williamson SR: Modern pathologic diagnosis of renal oncocytoma. J Kidney Cancer VHL 2017;4:1–12.

Yang JC, Haworth L, Sherry RM, et al: A randomized trial of bevacizumab, an anti–vascular endothelial growth factor antibody, for metastatic renal cancer. New Engl J Med 2003;349:427–434.

Zaid HB, Parker WP, Safdar NS, et al: Outcomes following complete surgical metastasectomy for patients with metastatic renal cell carcinoma: A systematic review and meta-analysis. J Urol 2017;197:44–49.

Zbar B, Brauch H, Talmadge C, et al: Loss of alleles of loci on the short arm of chromosome 3 in renal cell carcinoma. Nature 1987;327:721–724.

Zbar B, Tory K, Merino M, et al: Hereditary papillary renal cell carcinoma. J Urol 1994;151:561–566.

Zhan R, Li Y-Q, Chen C-Y, et al: Primary kidney malignant epithelioid angiomyolipoma: Two cases report and review of literature. Medicine (Baltimore) 2018;97.

Zinn AB, Kerr DS, Hoppel CL: Fumarase deficiency: A new cause of mitochondrial encephalomyopathy. New Engl J Med 1986;315:469–475.

Znaor A, Lortet-Tieulent J, Laversanne M, et al: International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol 2015;67(3):519–530.

Cancer of the Prostate Gland

21

Matthew R. Cooperberg, MD, MPH;
Samuel L. Washington III, MD;
& Peter R. Carroll, MD, MPH

CANCER OF THE PROSTATE GLAND

Incidence and Epidemiology

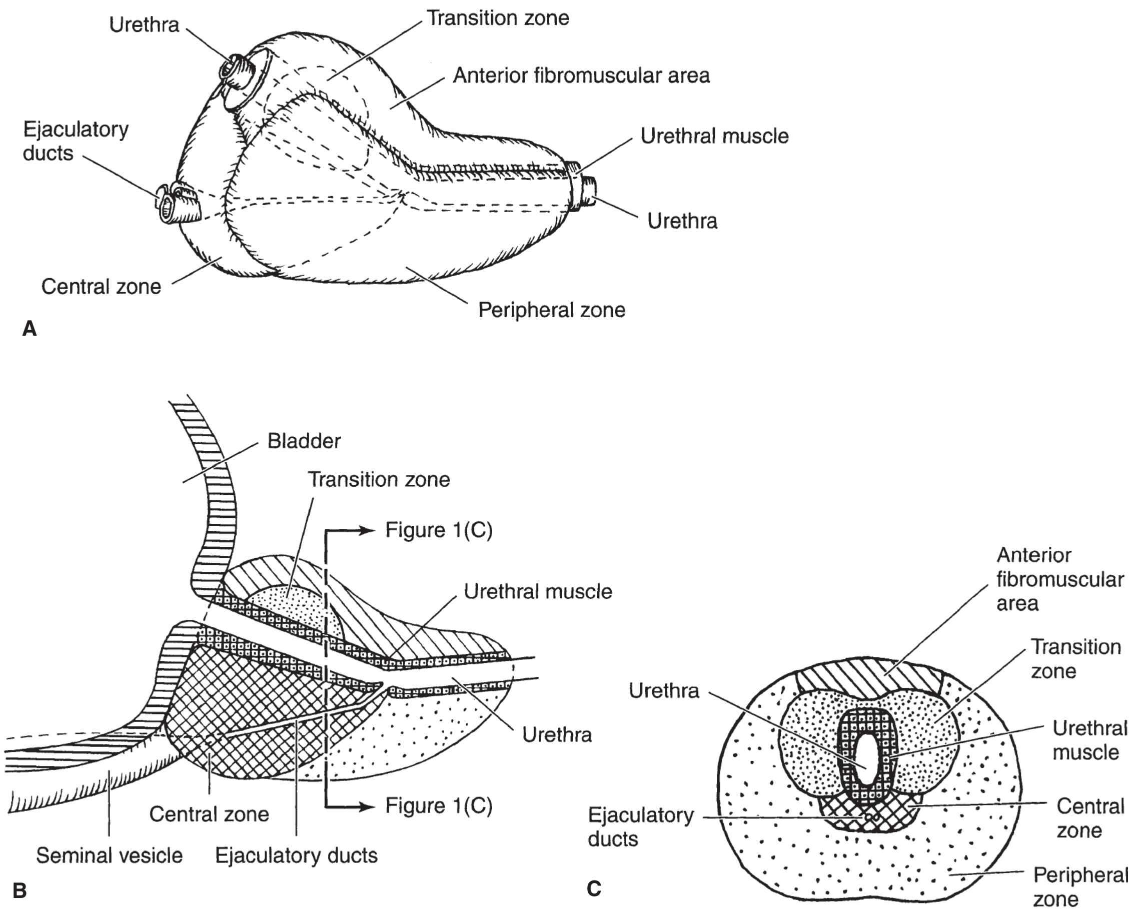
Prostate (see images of the prostate gland in Figures 21–1 and 21–2) cancer is the most common noncutaneous cancer detected among American men. More than 174,000 cases are detected annually (Siegel et al, 2019). Over 31,000 men die of the disease annually—the second highest burden among malignancies affecting men (Siegel et al, 2019). However, age-adjusted prostate cancer mortality at the population level has declined by roughly 50% since the mid-1990s, during a time in which men have been living longer and therefore have been more likely to reach the older ages at which prostate cancer mortality would be expected to increase. The explanation is controversial but is likely multifactorial, reflecting in large part a combination of early detection programs and improvements in treatment (Etzioni et al, 2012).

These improvements in mortality have come at the cost of significant rates of overdiagnosis and overtreatment. The number of prostate cancer deaths annually is far outweighed by the number of diagnoses, and most men diagnosed ultimately die of other causes, most often cardiovascular disease (Lu-Yao et al, 2009). Of all cancers, the prevalence of prostate cancer increases the most rapidly with age. However, unlike most cancers, which have a peak age of incidence, the incidence of prostate cancer continues to increase with advancing age. The risk of latent prostate cancer (ie, detected as an incidental finding at autopsy, not related to the cause of death) by age 80 is 36% for Caucasian men and 51% for African-American men (Jahn et al, 2015). The lifetime incidence of diagnosed prostate cancer is 15%, and the mortality rate 2.9%. Thus, many prostate cancers are indolent and inconsequential to the patient while others are more virulent, and if detected too late or left untreated, they result in considerable morbidity and ultimately in death. This broad spectrum of biological activity can make decision making for individual patients difficult and highlights the critical need for accurate risk stratification of prostate cancers, which will be discussed in further detail later.

Several risk factors for prostate cancer have been identified. As discussed earlier, increasing age heightens the risk for prostate cancer. Which factors associated with the aging process are responsible for this observation is unknown. The probability of prostate cancer diagnosis in a man younger than 40 years is 1 in 10,000; for men 40–59 years old, it is 1 in 103; and for men 60–79 years old, it is 1 in 8. African-Americans are at a higher risk for both incidence and mortality from prostate cancer than are Caucasians (Kelly et al, 2017). African-Americans tend to present with higher-grade and higher-stage disease—likely reflecting a ~5–10-year earlier onset of disease (Tsodikov et al, 2017), but in most studies race is not an independent predictor of lethal disease after controlling for stage and grade.

A positive family history of prostate cancer also increases the relative risk for prostate cancer. The age of disease onset in a family member with the diagnosis of prostate cancer affects a patient's relative risk. If the age of onset is 70 years, the relative risk is increased fourfold; if the age of onset is 60 years, the relative risk is increased fivefold; and if the age of onset is 50 years, the relative risk is increased sevenfold. Benign enlargement or growth of the prostate is not a risk factor for prostate cancer, although it does tend to raise the PSA level and increases the likelihood of consulting a urologist, which may increase the likelihood of prostate cancer diagnosis.

Although diagnostic biases due to varying penetrance of PSA screening exist across countries, differences in the incidence of prostate cancer are real. This variation may be related, in part, to differences in diet and other lifestyle factors. Epidemiologic studies have shown that the incidence of clinically significant prostate cancer is much lower in parts of the world where people subsist on a predominantly



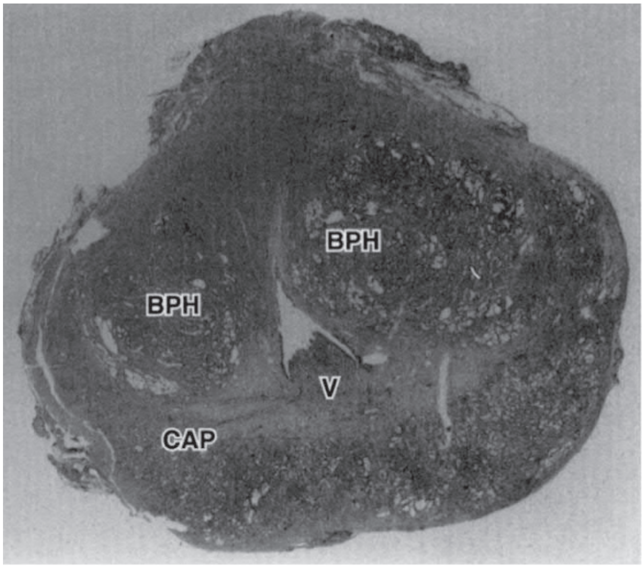
▲ **Figure 21–1.** ***A:*** Schematic lateral view of the prostate. ***B:*** Cut section of the same. ***C:*** Transverse view of area shown in ***B***.

low-fat, plant-based diet. In addition, migrant studies demonstrate that when men from a low-risk country move to the United States and begin adhering to a Westernized diet, their rates of prostate cancer increase several-fold, approaching those of the host country (Maskarinec G et al, 2004). Total fat intake, animal fat intake, and red meat intake are associated with an increased risk of prostate cancer, whereas intake of fish is associated with a decreased risk.

There is considerable controversy on the impact of obesity on prostate cancer. Some studies suggest that obesity is associated with an increased risk of more advanced disease and a higher recurrence rate after treatment (Vidal and Freedland, 2017). In addition, dietery lycopene, selenium, omega-3 fatty acids (fish), and vitamin E intake have been shown to be protective, whereas vitamin D and calcium increase risk. On the other hand, no dietary supplementation study has yet shown a tangible benefit in terms of reducing risk of diagnosis or mortality, and some supplements—most notably selenium—actually increase the risk of prostate cancer mortality (Kenfield et al, 2015). Adherence to a healthy lifestyle, defined by not smoking, adhering to a diet high in tomatoes and fatty fish, and maintaining a healthy weight and high physical activity level can reduce the risk of prostate cancer mortality by up to 68% (Kenfield et al, 2015). More frequent ejaculation has also been associated with a lower risk of prostate cancer diagnosis after controlling extensively for other factors in a large, prospective cohort study (Rider et al, 2016).

▶ Pathology

More than 95% of prostate cancers are adenocarcinomas. The histology of the remaining 5% of prostate cancer is heterogeneous, arising from stromal, epithelial, or ectopic cells. Nonadenocarcinoma variants can be categorized into two groups according to cellular origin: epithelial and nonepithelial. Epithelial variants consist of mucinous, signet-ring, adenoid cystic, adenosquamous, squamous cell, transitional cell, and neuroendocrine carcinoma and comedocarcinoma.



▲ **Figure 21–2.** Whole mount of prostate at level of midprostatic urethra. Note verumontanum (V) and areas of prostate cancer (CAP) in peripheral zone and areas of benign prostatic hyperplasia (BPH) in the transition zone.

Nonepithelial variants include rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma, carcinosarcoma, malignant lymphoma, and metastatic neoplasms, among others.

The remainder of this discussion focuses on adenocarcinoma. However, it is increasingly evident that neuroendocrine (small-cell) differentiation may occur in response to prolonged androgen deprivation. This can be recognized by staining such tissue for neuroendocrine markers (chromogranin A, neuron-specific enolase) and/or by measuring such markers in serum.

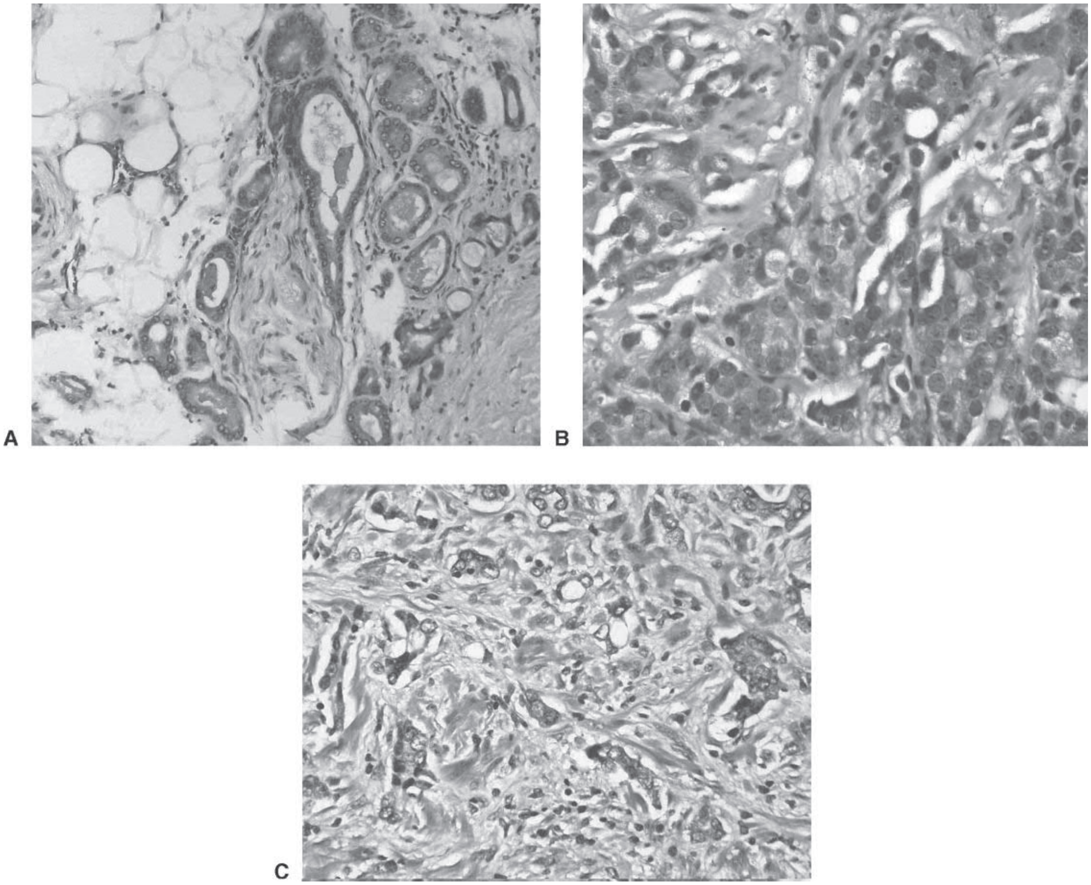
The cytologic characteristics of prostate cancer include hyperchromatic, enlarged nuclei with prominent nucleoli (Figure 21–3). Cytoplasm is often abundant; thus, nuclear-to-cytoplasmic ratios are rarely helpful in diagnosing prostate cancer, unlike their usefulness in diagnosing many other neoplasms. The diagnosis of prostate cancer is truly an architectural one. The basal cell layer is absent in prostate cancer, whereas it is present in normal glands, BPH glands, and the precursor lesions of prostate cancer. If the diagnosis of prostate cancer is in question, high-molecular-weight keratin immunohistochemical staining is useful, as it preferentially stains basal cells. Absence of staining is thus consistent with prostate cancer.

Prostatic intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP) are thought to be possible precursor lesions, and the risk of prostate cancer appears to be higher in those with the latter histology. Men with ASAP may warrant repeat biopsy, particularly if an extended-core biopsy was not performed initially. High-grade PIN (HGPIN) is characterized by cellular proliferations within preexisting ducts and glands, with nuclear and nucleolar enlargement similar to prostate cancer. However, unlike cancer, HGPIN retains a basal cell layer identifiable by immunohistochemistry.

Approximately 60–70% of cases of prostate cancer originate in the peripheral zone, 10–20% originate in the transition zone, and 5–10% originate in the central zone (see images of the prostate gland in Figures 21–1 and 21–2). Although prostate cancer is frequently multifocal, the use of widespread screening and extended biopsy techniques has resulted in the increasing detection of unifocal and smaller cancers.

Penetration of the prostatic capsule by cancer is a common event and often occurs along perineural spaces. Seminal vesicle invasion is associated with a high likelihood of regional or distant disease. Locally advanced prostate cancer may invade the bladder trigone, resulting in ureteral obstruction. Rectal involvement is rare, as Denonvillier's fascia represents a consistent barrier. (Of note, this barrier is largely one-way, as rectal cancer may invade the prostate or bladder relatively commonly.) Lymphatic metastases are most often identified in the obturator, external iliac, and internal iliac lymph node chains. Other sites of nodal involvement include the common iliac, perirectal, presacral, and periaortic lymph nodes, or less commonly the inguinal or chest nodes.

The axial skeleton is the most usual site of distant metastases; the lumbar spine is most frequently implicated (Figure 21–4). The next most common sites in decreasing order are the proximal femur, pelvis, thoracic spine, ribs, sternum, skull, and humerus. The bone lesions of metastatic prostate cancer are typically osteoblastic and sclerotic.



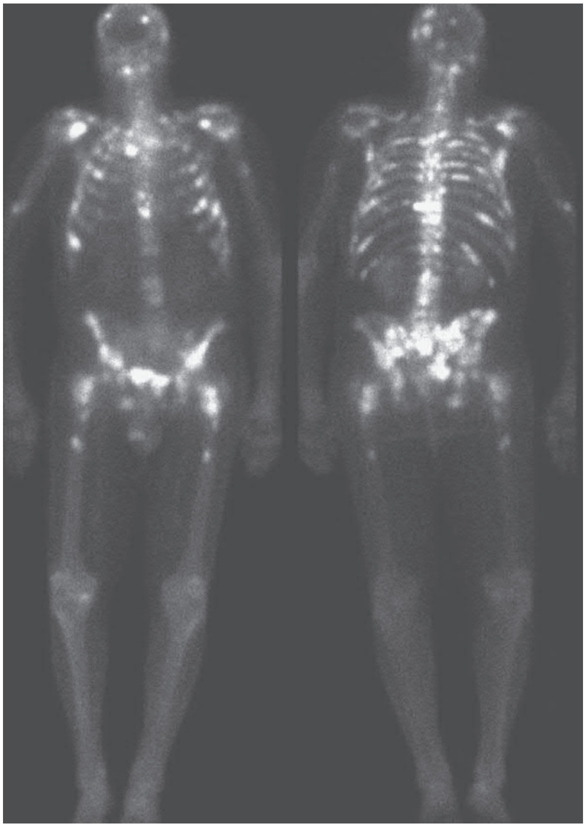
▲ **Figure 21–3.** Gleason primary grade 3 (***A***), grade 4 (***B***), and grade 5 (***C***) cancer (200×). ***A:*** Glands are well developed with variation in contour and morphology. The glands grow in an infiltrative pattern. Nuclear features of malignancy include mild nuclear enlargement, granular chromatin, and nucleoli. ***B:*** Malignant cells have trabecular, glandular, and infiltrative growth pattern forming small solid nests and abortive, fused glandular lumens. Malignant nuclear features include marked nuclear enlargement and macronucleoli. ***C:*** Highly infiltrative growth pattern with single cells and small nests of malignant epithelial cells. Cytologic features include marked nuclear pleomorphism and anisonucleosis with irregular contours, coarse irregular chromatin distribution, and macronucleoli.

Involvement of weight-bearing bones can lead to pathologic fractures. Vertebral body involvement with significant tumor masses extending into the epidural space can result in cord compression, which is a urologic emergency. Visceral metastases most commonly involve the lung, liver, and adrenal gland. Central nervous system (CNS) involvement is usually a result of direct extension from skull or spine metastasis.

▶ Molecular Genetics and Pathobiology

Chromosomal rearrangements or copy number abnormalities at 8p, 10q, 11q, 13q, 16q, 17p, and 18q have been described in prostate cancers. Some of these, such as specific loss at 8p23.2 and/or gain at 11q13.1, are predictive of prostate cancer progression.

Two transcription factors, ERG and EtV1, are often overexpressed in prostate cancer tissue. In many cases, the androgen responsive element TMPRSS2 is fused to these genes, driving their overexpression. This genetic rearrangement appears to be the most common one identified in prostate cancer. The TMPRSS2:ERG fusion has been identified in approximately 50% of prostate tumors and likely represents an early molecular event in carcinogenesis. Furthermore, this fusion may yield a distinct phenotype with a more aggressive natural history, independent of Gleason grade (Narod et al, 2008).



▲ **Figure 21–4.** Whole-body bone scintigram showing multiple bone metastases.

A subset of prostate cancers are driven by mutations in BRCA2 and other DNA repair pathway genes. Men with strong family histories of prostate, breast, and ovarian cancers should consider germline testing for these mutations (Giri et al, 2018). Recent studies have identified variations in RNA expression patterns notably similar to the basal, luminal A, and luminal B patterns previously documented in breast cancer (Zhao et al, 2017). Other in-depth expression analyses have demonstrated substantial variation in genomic expression not only among metastatic prostate cancer (Quigley et al, 2018) but also in localized cases (Lalonde et al, 2017), even those that appear low-risk from a clinical standpoint (Cooperberg et al, 2018).

▶ Clinical Findings

A. Symptoms

The vast majority of patients with early-stage prostate cancer are asymptomatic. The presence of symptoms usually suggests locally advanced or metastatic disease. Obstructive or irritative voiding complaints, including hematuria, can result from local growth of the tumor into the urethra or bladder neck or from its direct extension into the trigone of the bladder. Much more commonly, however, such symptoms are attributable to coexisting benign prostatic hyperplasia. Metastatic disease to the bones may cause bone pain. Metastatic disease to the vertebral column with impingement on the spinal cord may be associated with symptoms of cord compression, including paresthesias and weakness of the lower extremities and urinary or fecal incontinence.

B. Signs

A physical examination, including a digital rectal exam (DRE), is important. Induration or nodularity, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (ie, PSA, transrectal ultrasound [TRUS], and biopsy); however, most prostate cancers are not palpable at diagnosis, and a negative DRE does not obviate the need for further evaluation in men with elevated PSA. Locally advanced disease with bulky regional lymphadenopathy may lead to lymphedema of the lower extremities. Specific signs of cord compression relate to the level of the compression and may include weakness or spasticity of the lower extremities and a hyperreflexic bulbocavernosus reflex.

C. General Laboratory Findings

Azotemia can result from bilateral ureteral obstruction either from direct extension into the trigone or from retroperitoneal adenopathy. Anemia may be present in metastatic disease. Alkaline phosphatase may be elevated in the presence of bone metastases. Serum acid phosphatase may be elevated with disease outside the confines of the prostate.

D. Prostate-Specific Antigen and Other Tumor Markers

Prostate-specific antigen is a serine protease in the human kallikrein (HK) family produced by both benign and malignant prostate tissues. It circulates in the serum as uncomplexed (free or unbound) or complexed (bound) forms. PSA is used as a diagnostic (screening) tool, for risk-stratifying known prostate cancers, and for following cancers after treatment. As discussed earlier, PSA is *prostate*-specific, not *prostate cancer*-specific. Other prevalent conditions such as BPH and prostatitis—as well as urethral instrumentation and perineal insults such as prolonged bike riding—can elevate the PSA, producing false-positive results.

A "normal" PSA has traditionally been defined as ≤4 ng/mL, and the positive predictive value of a serum PSA between 4 and 10 ng/mL is approximately 20–30%. For levels in excess of 10 ng/mL, the positive predictive value increases from 42% to 71.4%. However, over the years it has become clear that the there is no single "normal" threshold for PSA; PSA varies as a continuous variable, reflecting age, prostate size, and risk of prostate cancer. The results of the Prostate Cancer Prevention

Trial (PCPT) study, which included biopsy regardless of PSA level—thus avoiding the ascertainment bias otherwise confounding virtually all other studies of PSA—demonstrated that there is no level of PSA below which prostate cancer risk falls to zero. PSA is rather indicative of a continuum of risk—the higher the level, the higher the risk (Thompson et al, 2007). Recent population studies have shown repeatedly that the median PSA among men between ages 45 and 55 years is approximately 0.7 ng/mL, and that for men with a PSA of <1.0 ng/mL a substantial majority across all age groups, the risk of progressive prostate cancer over the subsequent 25 years is extremely low (Preston et al, 2018; Vickers et al, 2013).

Current prostate cancer screening and detection strategies therefore include with PSA other risk factors such as family history, race, and age (Carter et al, 2013). Online risk calculators integrating these variables have been generated to determine risk of prostate cancer and risk of high-grade prostate cancer. A calculator based on the PCPT data, for example, is available at http://tinyurl.com/caprisk.

Use of medications such as 5α-reductase inhibitors (including the 1 mg finasteride formulation, Propecia, marketed for alopecia) must be ascertained, as these medications can artificially lower the PSA by approximately 50%. Serum PSA levels have also been noted to be decreased in men with high body mass indexes compared with normal weight men, likely as a result of hemodilution (Bañez et al, 2007).

Numerous strategies to refine PSA for detection of clinically significant prostate cancer have been explored. Their common goal in general has been to reduce overdetection and overtreatment by decreasing the number of false-positive test results, thus increasing the specificity and positive predictive value of the test for high-grade lesions and leading to fewer unnecessary biopsies, lowering costs, and reducing the morbidity associated with cancer detection. Attempts at refining PSA have included PSA velocity (PSAV) (change of PSA over time), PSA density (standardizing levels in relation to the size of the prostate), and PSA isoforms (free vs protein-bound molecular forms of PSA).

1. PSA kinetics—PSAV refers to the rate of change of serum PSA; its inverse, PSA doubling time (PSADT) indicates the amount of time required for the PSA to double. A retrospective study has shown that men with prostate cancer have a more rapidly rising serum PSA in the years before diagnosis than do men without prostate cancer. Patients whose serum PSA increases by 0.75 ng/mL per year appear to be at an increased risk of harboring cancer. However, PSAV must be interpreted with caution. An elevated PSAV should be considered significant only when several serum PSA assays are carried out by the same laboratory over a period of at least 18 months. Very rapid PSA increases may be indicative of prostatitis (symptomatic or otherwise) rather than cancer. Recent studies have questioned whether PSA kinetics in fact add significantly to the absolute PSA level in the prediagnosis setting (Vickers et al, 2011), and the optimal use of PSA kinetics remains controversial.

2. PSA density—PSA levels are elevated on average approximately 0.12 ng/mL per gram of BPH tissue. Thus, patients with enlarged glands due to BPH may have elevated PSA levels. The ratio of PSA to gland volume is termed the **PSA density**. Some investigators advocate prostate biopsy only if the PSA density exceeds 0.1 or 0.15, while others have not found PSA density to be useful. PSAD requires either a TRUS or MRI for an accurate assessment of volume.

3. Molecular isoforms of PSA—Various molecular isoforms of PSA have been identified and studied. Approximately 90% of the serum PSA is bound to α_1-antichymotrypsin (ACT), and lesser amounts are free or are bound to α_2-macroglobulins. In the latter form, no epitopes to the antibodies used in the current assays are available, while PSA-bound ACT may have three of its five epitopes masked. In men with a normal DRE and a total PSA level between 4 and 10 ng/mL, a 25% free PSA (fPSA) cutoff would detect 95% of cancers while avoiding 20% of unnecessary biopsies (Catalona et al, 1998). The predictive utility of percentage of fPSA in subsequent studies, however, has been mixed.

More recently, fPSA has been combined with other PSA isoforms to further improve prediction. A panel combining total PSA, fPSA, intact PSA, and hK2 (4K, OPKO Diagnostics) also integrates age, family history, race, and DRE findings to predict likelihood of aggressive prostate cancer. Another test combines total PSA, fPSA, and a truncated isoform designated −2proPSA, to yield a combined score marketed as Prostate Health Index (phi, Beckman Coulter). Both are able to significantly reduce biopsy rates while missing relatively few aggressive prostate cancers (Nordström et al, 2015).

4. PCA3—Prostate cancer antigen 3 (PCA3) is a noncoding, prostate-specific mRNA, which is overexpressed in the majority of prostate cancers, with a median 66-fold upregulation compared with adjacent noncancer tissue (Hessels et al, 2007). PCA3 predicts the presence of cancer in a biopsy setting with an accuracy of 74.6% (Groskopf et al, 2006). PCA3 may be particularly useful in the evaluation of men with a negative prior biopsy and a rising PSA (Haese et al, 2008). Like PSA, PCA3 reflects the spectrum of prostate cancer biology and does not perform optimally with a single threshold. In fact, PCA3 above 60 has a positive predictive value of 80% in the initial biopsy setting, while a PCA3 below 20 has a negative predictive value of 88% in the repeat biopsy setting (Wei et al, 2014).

5. SelectMDx—Another, more recently released, urine test marketed as SelectMDx (MDx Health) measures HOXC6 and DLX1 mRNA in the post-DRE urine. Combined with clinical parameters such as PSA, PSAD, prior biopsy history, and race, this test is able to achieve a very high NPV for clinically significant prostate cancer; at a threshold corresponding to an NPV of 98%, unnecessary biopsies could be reduced by over 50% (Van Neste et al, 2016).

6. ExoDx Prostate IntelliScore (Exosome Diagnostics, Inc., Waltham, MA)—Exosomes exist as small nanovesicles that are produced by normal and cancer cells and secreted into urine and blood. By measuring levels of urine exosomal ERG and PCA3 RNA without the need for a prior DRE, this test offers an additional predictive value above that of PSA, age, race, and family history to predict high-grade prostate cancer. The exosomes exist as small nanovesicles that are produced by normal and cancer cells and secreted into urine and blood (McKiernan et al, 2016). A prospective study that combined the test with clinical factors showed improved predictive accuracy compared to existing nomograms (AUC 0.73, 95% CI: 0.68–0.77) (McKiernan et al, 2016). The authors found that the test would prevent 27% of biopsies while missing 8% of high grade cases.

Very few high-quality studies have compared any of these emerging tests head to head.

Diagnosis and Evaluation

A. Prostate Biopsy

Prostate biopsy should be considered in men with an elevated serum PSA, abnormal DRE, or a combination of the two, depending additionally on the patient's overall health, comorbidities, life expectancy, levels of anxiety and of risk aversion, age, and information preferences. Prostate biopsy is performed under TRUS guidance using a spring-loaded biopsy device coupled to the imaging probe. A growing proportion of these biopsies are also guided by prior MRI, discussed further under imaging (section C) below. Break before biopsies are taken throughout the peripheral zone of the prostate, with optional additional sampling of any abnormal areas on DRE and/or TRUS. Increasing the number (≥10) and performing more laterally directed biopsies of the peripheral zone will increase detection rates 14–20% over the more traditional sextant technique. Although a small number of prostate cancers will originate in the transition zone, specific transition zone biopsies add little to overall cancer detection rates when an extended-pattern biopsy is performed. Some practitioners do add biopsies of the anterior commissure, a relatively frequent site of initially missed cancers found on second or subsequent biopsy (Meng et al, 2003). Break before there is ongoing interest in the use of even more extended biopsy schemes ("saturation biopsy") or use of a transperineal approach to improve cancer detection, usually in those who have had a negative biopsy, but are thought to be at an increased risk of prostate cancer based on a persistently abnormal serum PSA. Transperineal biopsy reduces the risk of sepsis compared to transrectal biopsy, although at the expense of higher risks of urinary retention. Achieving adequate anesthesia for transperineal biopsy is more difficult in the office setting but is possible and is being done in a growing number of practices.

Prostate biopsy is usually performed using local anesthesia and preprocedure antibiotic prophylaxis. The use of local anesthesia, either applied topically along the anterior rectal wall, injected into or adjacent to the prostate, or a combination of the two, decreases periprocedural discomfort and should always be used. Postprocedural hematospermia, hematochezia, and hematuria are very common and usually self-limited. With the rising prevalence of antibiotic-resistant bacteria, rates of sepsis despite standard prophylaxis have been growing (Lange et al, 2009). These can be life-threatening even in otherwise healthy men, and patients are counseled to return immediately to the emergency department for any fevers over 101°F after the procedure.

Most biopsy templates today include medial and lateral sampling of the apex, midgland, and base on the right and left sides. Given the known possibility of missed anterior tumors, some templates routinely include sampling the anterior apex. It is essential that the biopsy cores be adequately spread out to sample the far lateral and apical zones in particular, as tumors are easily missed in these locations.

Saturation schemes consist of 20 or more cores that emphasize sampling of the peripheral zone. One of the more common saturation schemes involves taking two cores from the lateral base, three cores from the lateral midgland, three cores from the apex (including the anterior apex), and one core from the parasagittal midgland and one core from the parasagittal base. While initial saturation schemes included two cores at both the parasagittal (medial) midgland and parasagittal base, unique identification of cancer in these areas is rare, and thus it has been recommended to obtain only one core for each of these areas. Investigators have demonstrated that saturation biopsies can be performed in the office using a periprostatic block. They observed no improved yield by using a saturation biopsy as the initial biopsy scheme or the first repeat biopsy scheme but rather advocate it as a second repeat biopsy strategy (Jones et al, 2002).

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial allowed examination of both cancer detection rates and grades and locations of cancers in a repeat biopsy situation. Entry criteria for this trial mandated a prior negative biopsy (minimum of a negative sextant biopsy) within 6 months of enrollment. In the placebo arm, 3346 patients underwent a repeat biopsy within 1–2 years of enrollment and 17.2% were found to have cancer, 30% of which were high-grade (Gleason score >7). At the repeat biopsy between years 3 and 4, 11.7% of 2343 patients were found to have cancer, 21% of which were high-grade. Considering only patients with primary Gleason pattern 4 or 5, 8.7% and 2.6% of the cancers were high-grade at the 2- and 4-year biopsy, respectively. This study also compared the relative merit of PCA3 and %fPSA in the repeat biopsy population. No significant difference was seen between these two markers for predicting cancer (Andriole et al, 2009).

B. Grading and Staging

The Gleason system is the most commonly employed grading system. The system relies on the low-magnification appearance of the glandular architecture under the microscope. In determining the grade of a given tumor, pathologists assign a primary grade to the pattern of cancer that is most commonly observed and a secondary grade to the second most commonly observed pattern in the specimen. Grades traditionally ranged from 1 to 5 (Figure 21–3). If the entire specimen has only one pattern present, then both the primary and secondary grades are reported as the same grade (eg, 3 + 3). The **Gleason score** or **Gleason sum** is obtained by adding the primary and secondary grades together.

However, pathology grading practices have changed over time, such that Gleason patterns 1 and 2 are rarely assigned, so **Gleason pattern 3** corresponds to low-grade disease (variable-sized glands that percolate through normal stroma and between normal glands), **Gleason pattern 4** corresponds to intermediate-grade disease (incompletely formed glands with variable amounts of fusion and more infiltrative growth pattern), and **Gleason pattern 5** corresponds to high-grade disease (single infiltrating cells with no gland formation). Variations in growth such as cribriform patterns and comedocarcinoma are also observed; expansile cribriform morphology and intraductal carcinoma are notably more aggressive subtypes usually grouped with Gleason pattern 4.

A Gleason score 6 (3 + 3) tumor is uniformly low-grade. In differentiating intermediate- and high-grade tumors, the primary Gleason pattern is the most important determinant of biologic risk. Thus, among Gleason score 7 tumors, those assigned 4 + 3 are more aggressive than those read as 3 + 4. The extent of high-grade (ie, pattern 4 or 5) cancer may be the primary driver of outcome, and prediction can be improved by quantifying the amount of high grade rather than reporting simply 3 + 4 or 4 + 3 (Catalona et al, 1998).

In contemporary practice, Gleason scores are grouped such that Gleason 3 + 3 or lower corresponds to group 1, Gleason 3 + 4 to group 2, Gleason 4 + 3 to group 3, Gleason 8 to group 4, and Gleason 9–10 to group 5 (Epstein et al, 2016). This new system represents a change in nomenclature rather than any substantial change in pathologic assessment. However, it is more intuitive to patients since the lowest stratum is grade group 1 out of 5, rather than Gleason sum 6 out of 10. The new system has the further advantage that Gleason 3 + 4 and 4 + 3 can no longer be grouped as "Gleason 7." Within the new grade group 5, tumors with primary Gleason pattern 5 (ie, 5 + 4 and 5 + 5) may have a worse prognosis than Gleason 4 + 5 tumors, but most analyses are limited by small numbers of men with these highest tumor grades (Leapman et al, 2017).

The AJCC TNM staging system for prostate cancer is presented in Table 21–1. Note that with respect to the primary tumor categorization (T stage), the clinical staging system uses results of the DRE, but not the results of imaging or biopsy in differentiating T1 and T2 disease. The clinical stage of a patient who has a palpable abnormality on one side of the prostate, even though biopsies demonstrate bilateral disease remains T2a. It should be noted that compared with risk factors such as Gleason score and PSA levels, clinical T stage in prostate cancer is a relatively weak prognostic factor. Partly because of the subjectivity of DRE and TRUS interpretation, and given adjustment for more objective measures of tumor volume such as percent of biopsy cores involved, T stage often drops out of multivariable models of prostate cancer prognosis, at least among T1 and T2 tumors which account for the vast majority of tumors diagnosed in contemporary practice (Reese et al, 2010).

Table 21–1. TNM staging system for prostate cancer.

T—Primary tumor	
Tx	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (PIN)
T1a	≤5% of tissue in resection for benign disease has cancer, normal DRE
T1b	>5% of tissue in resection for benign disease has cancer, normal DRE
T1c	Detected from elevated PSA alone, normal DRE and imaging
T2a	Tumor palpable by DRE or visible by imaging, involving less than half of one lobe of the prostate
T2b	Tumor palpable by DRE or visible by imaging, involving more than half of one lobe of the prostate
T2c	Tumor palpable by DRE or visible by imaging, involving both lobes of the prostate
T3a	Extracapsular extension on one or both sides
T3b	Seminal vesicle involvement on one or both sides
T4	Tumor directly extends into bladder neck, sphincter, rectum, levator muscles, or into pelvic sidewall
N—Regional lymph nodes (obturator, internal iliac, external iliac, presacral lymph nodes)	
Nx	Cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a regional lymph node or nodes
M—Distant metastasis	
Mx	Cannot be assessed
M0	No distant metastasis
M1a	Distant metastasis in nonregional lymph nodes
M1b	Distant metastasis to bone
M1c	Distant metastasis to other sites

DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

Used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) *AJCC Cancer Staging Manual,* 8th Ed. Springer New York, 2017.

C. Imaging

1. TRUS—In an era of increasing use of MRI, TRUS is often denigrated as a means only of directing biopsies to regions of the prostate. However, with modern equipment and experience, TRUS can be an excellent modality to both identify and stage prostate cancers, and a TRUS biopsy should always include a careful sonographic examination of the whole prostate gland. If visible, prostate cancer tends to appear as a hypoechoic lesion in the peripheral zone and/or hypervascularity seen on power Doppler examination. The sonographic criteria for extracapsular extension are bulging of the prostate contour or angulated appearance of the lateral margin. The criteria for seminal vesicle invasion are a posterior bulge at the base of the seminal vesicle or asymmetry in echogenicity of the seminal vesicle associated with hypoechoic areas at the base of the prostate.

2. Magnetic resonance imaging (MRI)—Multiparametric MRI (mpMRI) assessment of the prostate is growing rapidly in popularity. This exam includes T2-weighted anatomic imaging and diffusion-weighted imaging (DWI); the latter reflects the increased cell membrane density and resulting drop in water (hydrogen) density of cancer compared to normal tissue. The standard mpMRI exam also includes dynamic contrast enhancement (DCE) imaging, although this adds time and cost with a relatively low incremental benefit and is not included in all protocols.

Prostate mpMRI interpretation is standardized using Version 2 of the Prostate Imaging Reporting and Data System (PIRADS), under which radiologists summarize the T2, DWI, and DCE results into a 1–5 score. PIRADS 1 and 2 are predicted to exclude high-grade (Gleason grade group ≥2) cancer, 3 is indicative of possible high-grade cancer, and 4 and 5 indicate probable high-grade cancer (Zhang et al, 2017). While PIRADS does represent a consistent framework, interobserver variability has been studied only occasionally and is an issue at even high-volume centers (Greer et al, 2017). Therefore, mpMRI should be performed and read only by prostate-oriented subspecialists (Sonn et al, 2017).

Use of magnetic resonance spectroscopy (MRS) in conjunction with MRI may improve the accuracy of imaging. Prostate cancer is associated with proportionately lower levels of citrate and higher levels of choline and creatine compared with BPH or normal prostate tissue. The combined metabolic and anatomic information provided by a multiparametric MRI exam and MRS may allow for a more accurate assessment of cancer location and stage. Break before the reported staging accuracy of endorectal MRI varies from 51% to 92% (Nelson SJ et al, 2013). It appears to add novel information to the assessment of some patients over the use of nomograms alone, but it may be best utilized in high-risk patients where it is most accurate and helpful (Afnan and Tempany, 2012; Verma et al, 2010).

Magnetic resonance imaging (MRI) is particularly useful for identifying anterior lesions that are more difficult to detect by TRUS and is increasingly used to augment prostate biopsy. Urologists may reference MRI findings and images in advance of the biopsy and focus especially on areas identified on the MRI (**cognitive fusion**), or the MRI images can be overlaid in real time onto the TRUS using a variety of fusion-directed biopsy platforms. Finally, in some cases the biopsy can be performed with direct MRI guidance in an open-bore magnet. No one approach or technology has been shown convincingly to be better than the others (Wegelin et al, 2017, 2018). Some have suggested that fusion-directed biopsies can replace systematic biopsy altogether, and that a patient with an elevated PSA and a negative MRI can avoid the need for a biopsy (Kasivisvanathan et al, 2018). Such an approach will miss approximately a quarter of high-grade cancers, however (Ahmed et al, 2017). Although many controversies remain regarding the optimal use of MRI, at this point most feel MRI can augment TRUS-directed biopsy, may replace repeat biopsy for those with a prior negative biopsy, and may possibly play a role in active surveillance (Klotz et al, 2018; Tran et al, 2018) but cannot replace a first biopsy.

3. Axial imaging (CT, MRI)—Cross-sectional imaging of the pelvis in patients with prostate cancer is selectively performed to exclude lymph node metastases in high-risk patients who are thought to be candidates for definitive local therapy, whether it be surgery or irradiation. Both CT and body coil-based MRI are used for this purpose. Neither modality is particularly accurate for local T staging. Patients identified as having lymphadenopathy on imaging may occasionally undergo CT-guided fine-needle aspiration if the diagnosis is equivocal. Various criteria can be used to identify patients for axial imaging, including negative bone scans and either T3 cancers or a PSA of >20 ng/mL and primary Gleason grade 4 or 5 cancers. Like bone scan, cross-sectional imaging—CT in particular—is widely overused for staging of low-risk tumors that are very unlikely to be associated with lymph node metastases.

4. ^{99}Tc bone scan—When prostate cancer metastasizes, it most commonly does so to the bone (Figure 21–4). Soft-tissue metastases (eg, lung and liver) are rare at the time of initial presentation. Although a bone scan has been considered a standard part of the initial evaluation of men with newly diagnosed prostate cancer, good evidence has been accumulated that it can be excluded in most of these men on the basis of serum PSA. Bone scans unequivocally can be omitted in patients with newly diagnosed, untreated prostate cancer who are asymptomatic, have T1 and T2 disease, and have serum PSA concentrations of <20 ng/mL. These recommendations, in fact, are incorporated into clinical guidelines for the management of clinically localized prostate cancer, but bone scan remains widely overused among men with low-risk disease, as confirmed even in contemporary studies (Palvolgyi et al, 2011).

5. Positron emission tomography (PET) imaging—Identifying a metastasis by either CT or bone scan requires a mass of approximately 10^9 cells; thus, many high-risk cancers staged as “M0” are in fact micrometastatic. In recent years, several PET tracers have entered clinical practice for prostate cancer that promise greater sensitivity at lower tumor volumes. These tracers are being evaluated in various clinical settings, including use at the time of initial diagnosis, as part of active surveillance, and during the workup for potential metastatic disease to determine the optimal timing of usage. It should be emphasized, however, that nearly all clinical trials and other clinical studies as of 2019 continue to define "M0" and "M1"—as well as "oligometastatic"—based on traditional bone scan findings, not on any more advanced imaging.

18F sodium fluoride (NaF)—NaF PET scans have now been used for decades in the evaluation of osseous metastases from prostate cancer. While this modality has demonstrated a sensitivity of 93%, the specificity is significantly lower (54%) with a high rate of false-positive findings (Poulsen et al, 2014). A negative scan may still miss small metastatic lesions with limited radiotracer uptake. NaF PET is used relatively frequently, but its optimal role has never been clarified.

Choline and acetate—Prostate cancer cells are found to preferentially concentrate phosphocholine compared to normal prostate cells. Utilizing this knowledge, radiotracers bound to ^{11}C-choline can localize metastatic lesions (Ackerstaff et al, 2001). A whole-body tracer of ^{11}C-choline is administered to the patient and areas with increased focal uptake identified as suspected sites of metastatic disease. In a retrospective study of ultra-high-risk patients who underwent prostatectomy, choline PET had a reported sensitivity of 71% and a sensitivity of 92% for detection of lymph node metastases when compared to surgical pathology (Schiavina et al, 2018). Similarly, cancer cells have an increased cellular membrane lipid requirement, and acetate remains the single carbon source used by cancer cells for fatty-acid and cholesterol production (Yoshii et al, 2015). Studies evaluating its utility in assessing regional lymph nodal disease have reported modest sensitivity and specificity, 38–68% and 78–96%, respectively, with the caveat that it may be unable to identify smaller foci of nodal involvement (Haseebuddin et al, 2013; Daouacher et al, 2016).

Fluciclovine (Axumin)—18F-fluciclovine is a synthetic amino acid that is transported by numerous ion channels that are upregulated in prostate cancer cells (Okudaira et al, 2014). For men with a rising PSA after primary treatment (surgery or radiation), this radiotracer has been used to detect and localize sites of recurrence. Prior studies have reported a positive predictive value of 92.3–100% and a negative predictive value of 51.7% for extraprostatic disease (Odewole et al, 2016; Bach-Gansmo et al, 2017).

^{68}Ga PSMA—Prostate-specific membrane antigen is a transmembrane protein consistently present in most prostate cancers—and in the neovasculature of several other malignancies—and in few normal tissues aside from the salivary glands. A PSMA small-molecule ligand is radiolabeled with ^{68}Ga and used as a radiotracer to identify potential foci of nodal disease. This tracer has been evaluated in lymph node staging in the preoperative setting and in men with biochemical recurrence after prior treatment with a reported positive predictive value of 83% and negative predictive value of 80% for nodal staging (Herlemann et al, 2016). ^{68}Ga-PSMA PET scans have shown promise in identifying nodal and bone metastasis that would have otherwise been missed with conventional CT scans. In a retrospective study of 147 patients with biochemical recurrence, ^{68}Ga PSMA PET scans in 54–69% of cases were found to have undetected cN1 disease when compared to standard CT scans (Vinsensia et al, 2017). This agent is currently available in Europe and Australia, and is expected to be approved in the United States—along with at least two other PSMA-targeting PET tracers—in the very near future.

D. Multivariable Risk Assessment

As discussed elsewhere in this chapter, contemporary treatment patterns for prostate cancer are marked by both overtreatment of low-risk disease and undertreatment of high-risk disease. A key approach to mitigating this problem is better and more consistent risk stratification intended to help identify the best timing and intensity of treatment for a given patient. The critical variables for optimal risk stratification have been detailed earlier: the PSA level, the Gleason score, and some measure of tumor volume—clinical T stage and/or extent of biopsy core involvement (eg, percent of cores positive or percent of all biopsy tissue positive). More than 100 risk formulas, lookup tables, nomograms, and other instruments have been published to facilitate this task (Cooperberg, 2008; Shariat et al, 2008). Some key instruments are described as follows.

1. Risk groups—One of the first widely adopted approaches to risk stratification is a three-level risk group classification published by D'Amico et al and formally adopted by the AUA's practice guideline for localized prostate cancer treatment (Thompson et al, 2007; D'Amico, 2000). In this classification, men are assigned to one of three groups as follows:

Low risk—PSA ≤10, Gleason ≤6, and clinical stage T1 or T2a

Intermediate risk—PSA 10–20, Gleason 7, or clinical stage T2b

High risk—PSA >20, Gleason 8–10, or clinical stage T2c or T3a

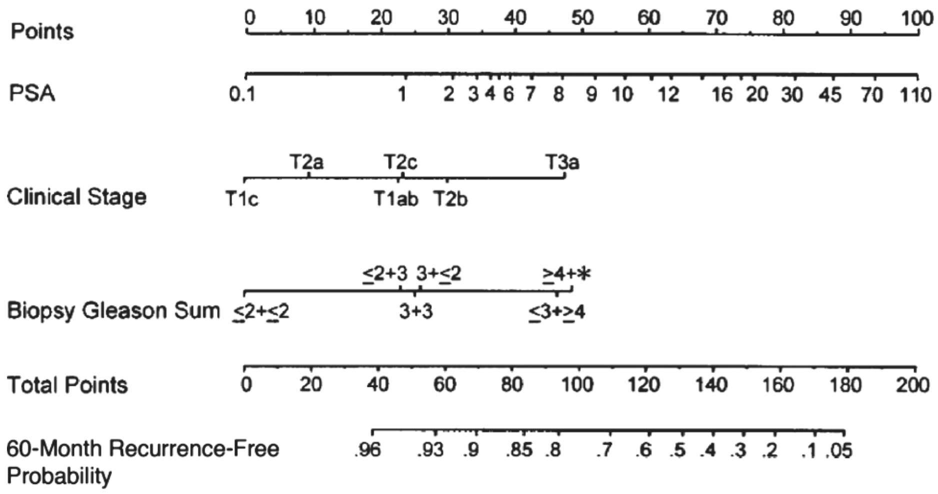
The major advantage of this system is its simplicity, and it is used very commonly. However, it has major drawbacks. First, it overweights the T stage, which, as noted earlier, is not an accurate measure of tumor extent within the T2 category. Second, it does not distinguish between Gleason 3 + 4 and 4 + 3 tumors, which (again, as noted earlier) have very different biologic activity levels, within the Gleason 7 category. Finally, and most importantly, it is not a true multivariable instrument in that it does not account for information from the various risk variables. For example, both a patient with PSA 19.8, Gleason 4 + 3, stage T2b tumor and a patient with

PSA 4.2, Gleason 3 + 4, stage T1c tumor are classified as "intermediate risk," despite expectations that these patients will have quite different trajectories in terms of disease burden and risk of progression. The AUA and NCCN have published subclassifications that attempt to provide more granularity, but these only partially address the problems noted above, and still are not linear predictors of outcome, and—through inconsistent consideration of different risk factors at each stratum of risk—have become increasingly cumbersome to apply in practice.

Risk group	D'Amico	NCCN	EAU	AUA
Very low		PSA < 10, PSAD < 0.15, cT1c, GG1, ≤3 cores positive, ≤50% of any core positive		PSA < 10, PSAD < 0.15, cT1c, GG1, ≤3 cores positive, ≤50% of any core positive
Low	PSA < 10, cT1/2a, GG1	PSA < 10, cT1/2a, GG1	PSA < 10, cT1/2a, GG1	PSA < 10, cT1/2a, GG1
Favorable intermediate	PSA 10–20, cT2b, GG2–3	PSA 10–20, cT2b–c, GG2–3	PSA 10–20, cT2b, GG2–3	PSA 10–< 20 + GG1 or PSA < 10 + GG2
Unfavorable intermediate				GG2 + PSA 10–<20 / cT2b–c or PSA < 20 + GG3
High	PSA > 20, cT2c, GG4–5	PSA > 20, cT3a, GG4–5	PSA > 20, cT2c, GG4–5 or any PSA, any GG, cT3–4, cN+	PSA > 20, ≥cT3, GG4–5
Very high		cT3b-4, ≥4 cores with GG4–5 or primary Gleason pattern 5		

2. Lookup tables and nomograms—Most risk instruments are based on multivariable logistic regression or Cox proportional hazards models depending on the outcome of interest. For example, the well-validated lookup tables first published by Partin et al predict pathologic outcomes such as extracapsular extension and seminal vesicle invasion (Makarov et al, 2007).

A nomogram is a graphical representation of a regression model. First popularized in urology by Kattan et al, nomograms are alternatives to lookup tables (see Figure 21–5).



▲ **Figure 21–5.** Kattan nomogram for predicting 5-year probability of biochemical recurrence-free survival.

To use a nomogram, a patient is assigned a number of points for each risk factor; the summed total score is then used to yield a prediction for the outcome of interest (eg, 5-year biochemical recurrence-free survival), usually with a ±10% margin of error (Kattan et al, 2003).

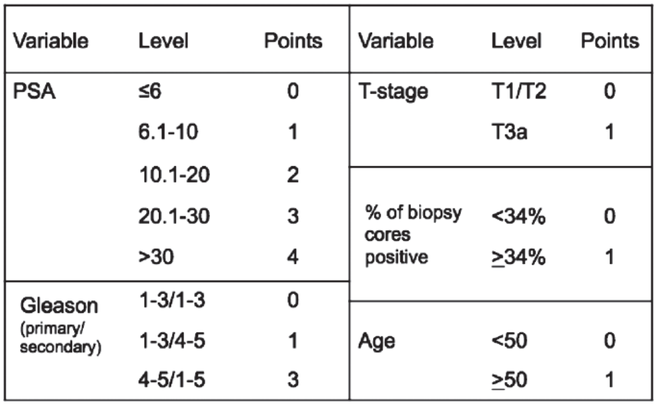
Multiple nomograms have been published for predicting pathologic outcomes, biochemical outcomes after surgery or radiation therapy, or longer-term outcomes such as progression-free survival, metastasis-free survival, or mortality (overall or cancer-specific). Two important caveats should be noted. First, a given nomogram is developed according from data on a specific cohort of men, usually treated in one or a few academic centers in which a small number of highly trained surgeons or radiation oncologists treat large volumes of patients. Preferably, the nomogram is then externally validated at other institutions and/or using different cohorts of patients. A great deal of caution must be exercised in calculating specific risks of recurrence for patients treated in settings outside of those used to develop and validate the nomogram, and ideally nomograms should be formally validated in a given setting before routine use in that setting.

Second, with more complex statistical software, it is very easy to calculate multiple nomogram scores simultaneously, creating a temptation to compare treatment options such as surgery or radiation using the nomogram scores. Nomograms cannot be used this way—the cohorts of patients used to develop each are very different, as are the definitions of the outcomes reported. Thus, nomograms may be useful to give a patient undergoing a specific treatment a sense of the probability of likely outcomes, but should not be used to as a method of comparison between treatments to guide clinical decisions, and one must consider the generalizability of the cohort in the development of the nomogram when counseling patients.

3. CAPRA score—Because of these limitations—and the fact that nomograms are difficult to calculate for hundreds or thousands of patients in research settings and cannot be used to consistently identify low- or high-risk cohorts—the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score was developed, intended to combine the accuracy of nomograms with the ease of calculation of a risk grouping system (Cooperberg et al, 2005). To calculate the CAPRA score, points are assigned primarily on the basis of the PSA and Gleason score, with lesser weights given to the T stage, percent of biopsy cores positive, and patient age (Figure 21–6).

Points are added to yield a 0–10 score. Overall, every 2-point increase in score (eg, from 2 to 4 or from 5 to 7) indicates roughly a doubling of risk. CAPRA scores in the 0–2 range indicate relatively low-risk disease, CAPRA 3–5 tumors are intermediate-risk, and CAPRA 6–10 tumors are high-risk. The CAPRA score has been extensively validated in the United States and Europe in multiple contexts (Bratjbord et al, 2017). It was found to offer better accuracy than competing instruments in an independent head-to-head comparison study (Lughezzani et al, 2010). Moreover, it has been shown to predict long-term metastasis and mortality—after surgery, radiation therapy, and hormonal therapy (Cooperberg et al, 2009)—ranging from essentially 0% to over 60%, with up to 85% accuracy. A postoperative version incorporating pathologic data (CAPRA-S) has also been published and extensively validated (Kattan et al, 2003; Lughezzani et al, 2010).

It is important to note that the CAPRA and CAPRA-S scores are primarily meant to indicate *relative* rather than absolute risk. Thus, a tumor with a CAPRA score of 4 has an intermediate risk of recurrence or progression after surgery or radiation. This tumor will be *more likely* to progress than one with a score of 2, and *less likely* than one with a score of 6, regardless of treatment approach or setting. The *specific* risk (eg, likelihood of disease-free status at 5 years after treatment), while roughly consistent across different cohorts, will depend substantially on factors such as surgeon skill and experience, pathology grading practices, and so on that are not incorporated in the calculation.



Variable	Level	Points
PSA	≤6	0
	6.1-10	1
	10.1-20	2
	20.1-30	3
	>30	4
Gleason (primary/ secondary)	1-3/1-3	0
	1-3/4-5	1
	4-5/1-5	3

Variable	Level	Points
T-stage	T1/T2	0
	T3a	1
% of biopsy cores positive	<34%	0
	≥34%	1
Age	<50	0
	≥50	1

▲ **Figure 21–6.** Cancer of the Prostate Risk Assessment (CAPRA) score criteria.

E. Other Biomarkers

Numerous diagnostic biomarkers have been developed and are performed on prostate biopsy specimens to provide information regarding risk of various clinical outcomes, including biochemical recurrence after primary treatment and prostate cancer-specific mortality. However, given the excellent accuracy of multivariable clinical risk tools such as the CAPRA score (up to 85% accuracy for predicting cancer-specific mortality), the bar is high for a candidate test to demonstrate improved prognostic ability. Moreover, the reporting format of a test in clinical practice may substantially distort its optimal impact on clinical decision making. Finally, even if a test is proved independently *prognostic*, meaning that it contributes additional incremental information about likelihood of cancer progression, it may or may not be *predictive* of response to any given intervention.

1. Prolaris (Myriad Genetics, Inc., Salt Lake City, UT)—This test predicts 10-year prostate cancer mortality using RNA expression from a panel of 31 cell cycle progression (CCP) genes and 15 housekeeping genes, quantified by reverse transcription polymerase chain reaction (RT-PCR) (Cuzick et al, 2011; Loeb and Ross, 2017). In the initial study higher cell cycle progression scores were associated with biochemical recurrence in men who underwent radical prostatectomy (Cuzick et al, 2011). A similar association was found between CCP scores based on biopsy specimens, as higher scores at biopsy were associated with biochemical recurrence on multivariable analysis (Bishoff et al, 2014). A later study showed that combining these cell cycle progression scores with CAPRA-S resulted in improvement in the predictive model for 10-year prostate cancer mortality (C-index increase from 0.74 to 0.78) (Cuzick et al, 2015). Others have demonstrated that it provides prognostic information not captured using established pretreatment clinical data for men treated with surgery or radiation (Bishoff et al, 2014; Tosoian et al, 2017; Freedland et al, 2013). A clinical genomic score that combines the CAPRA score and the CCP score offers excellent NPV for lethal disease within 10 years of diagnosis (Lin et al, 2018).

2. Oncotype Dx Genomic Prostate Score (GPS) (Genomic Health, Inc., Redwood City, CA)—The GPS score comprises a genomic panel of 12 associated with aggressive prostate cancer and 5 housekeeping genes, again based on measured RNA expression levels by RT-PCR (Loeb and Ross, 2017; Klein et al, 2014). The panel was initially selected according to ability to predict cancer-specific mortality across multiple foci of cancer within prostatectomy specimens, and has been validated for predicting adverse pathology (ie, pT3 or higher and/or Gleason grade group ≥ 3) on radical prostatectomy specimens using biopsy specimens. In a validation study using a cohort of 395 biopsy specimens, GPS was shown to be significantly associated with adverse pathology at time of prostatectomy beyond standard clinical and pathologic parameters (Klein et al, 2014). In a separate study, biopsy GPS was found to also predict biochemical recurrence in addition to adverse pathology at prostatectomy in a cohort of 431 men with grade group ≤ 2 at biopsy who went on to surgery (Cullen et al, 2015). However, although the test was shown to add independent information to validated multivariable models, its clinical report presents the score in context only of the NCCN risk groups, and in a format that can be misleading, reducing its clinical utility.

3. Decipher (Decipher Biosciences, Inc., San Diego, CA)—This genomic assay is based on a full transcriptome microarray and measures RNA expression levels from 22 genes to predict risk of early metastasis after radical prostatectomy (Loeb and Ross, 2017; Erho et al, 2013; Leapman et al, 2016). The score provided in the report can be used to stratify patients into low, average, and high genomic risk for high-grade disease at time of prostatectomy, 5-year metastasis, and 10-year prostate cancer not specific mortality. Like Prolaris and GPS, it has been demonstrated to add independent prognostic information beyond a multivariable clinical risk score (Ross et al, 2016; Cooperberg et al, 2015). A biopsy test has now been validated as well, and was shown to have similar utility with patients treated with primary radiation and androgen deprivation, as the score of biopsy tissue was found to be associated with an increased risk of distant metastasis at 5 years posttreatment (Nguyen et al, 2017). No published studies have compared Prolaris, GPS, and Decipher head to head. One advantage that Decipher offers, however, is that, because the whole transcriptome is measured, future tests based on the expression data already determined may be able to predict responses to other treatments such as radiation and hormonal therapy (Zhao et al, 2016; Karnes et al, 2018).

▶ Prostate Cancer Screening and Chemoprevention

The primary argument against screening is that many cancers identified through screening efforts would never result in clinically significant disease in the patient if left untreated, a phenomenon called **overdetection**. Some have estimated that between 23% and 42% of cancers detected by an aggressive screening program are such cancers (Draisma et al, 2009; Etzioni et al, 2002). Prostate cancer screening is a complex and often controversial topic, although in 2020 experts in primary care and urology/oncology seem to be closer to agreement that most men in good health, with at least a 10–15-year life expectancy, should be offered prostate cancer early detection through a process of shared decision making (SDM) between the patient and primary care provider. This discussion should address both the benefits and disadvantages of screening; in brief, early detection efforts reduce the risk of cancer mortality and its preceding morbidity by at least 30%, but at the cost of possible overdiagnosis of entirely indolent disease that would have caused no symptoms or threat to life if undetected. This underscores the importance of shared decision making before screening is undertaken and the need to discuss all treatment options, including active surveillance, in patients found to have the disease (Vickers et al, 2014a).

Most guidelines recommend that screening be offered to men aged 55–69 years in the setting of an SDM discussion (Vickers et al, 2014b), based in large part on the ERSPC trial (see discussion below). Others, however, advocate for earlier screening starting between ages 40 and 55 years, based on (1) less confounding of PSA assessment by BPH at earlier ages and (2) the fact that a small but significant number of men already have high-risk or advanced prostate cancer by their fifties. Some, but not all, guidelines assert that screening should start earlier for men with risk factors such as family history and/or African-American ethnicity. Although annual screening was previously recommended in the United States, some feel that men with very low serum PSA level (eg, ≤1 ng/mL) may be screened at much less frequent intervals (deferring a next test for at least 5–10 years) (Preston et al, 2018; Vickers et al, 2013). Similarly, if the PSA level remains <1 ng/mL by the age of 60, then the likelihood of death from prostate cancer by the age of 85 falls to well under 1% (Vickers et al, 2013).

Two large randomized screening trials initially reported in 2009 appeared to give contradictory results and further fueled the controversy around screening. With a repeated review of the data after longer follow-up, however, further publications have made clear that the results of the two may actually be consistent and compatible. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial randomized 76,693 men in the United States to annual PSA screening or usual care. The risk of prostate cancer death with 7–10 years' follow-up was very low in both screened and unscreened men and did not differ significantly between them. However, a very high proportion of men in the "control" arm of the study, in fact, were screened with PSA before the start of the study and/or during the study, and furthermore the rate of prostate biopsy among men who crossed the predefined PSA threshold of 4.0 ng/mL was quite low. These limitations, coupled with potential lead time bias associated with prostate cancer studies reporting outcomes over shorter follow-up intervals, limit the ability of this study to fairly test the hypothesis, and with subsequent publications the authors have asserted that the PLCO was not a trial of screening versus no screening, but rather annual organized screening versus ad hoc, or opportunistic, screening (Pinsky et al, 2017).

The European Randomized Study of Screening for Prostate Cancer (ERSPC) randomized 162,387 men in seven countries to PSA screening at 2- or 4-year intervals, with biopsy thresholds ranging from 2.5 to 4.0 ng/mL. This was a larger study than PLCO, with longer follow-up and much less contamination among control patients. The study demonstrated that screening was associated with a 20% relative reduction in prostate cancer-specific mortality at 9 years median follow-up. A follow-up analysis found that after adjusting for compliance with screening, the reduction in mortality rose to 29%. The hazard curves in the ERSPC study began to diverge only approximately 7 years into the trial; with longer follow-up, the benefit of screening is further magnified (Schroder et al, 2014).

A recent detailed analysis of contamination rates and lead times in both PLCO and ERSPC found that if these factors are adequately addressed, the results are highly comparable, with both trials reducing relative mortality risk by 25–31% (Tsodikov et al, 2017). In a third trial in Göteborg, Sweden—a subset of which patients were also contributed to the ERSPC—a high rate of compliance, low rates of testing in the control arm, and a younger median age (56) at enrollment, drove a mortality reduction was nearly 50% with 14-year follow-up (Hugosson et al, 2010).

Chemoprevention

There is much interest in prostate cancer prevention due to the disease's high prevalence, slowly progressive nature, long latency period, and high absolute mortality. The ideal therapeutic intervention would arrest disease progression during the latency period and decrease the incidence of clinically significant disease. The ideal agent should be nontoxic and of low cost, and the ideal patient would be one at high risk of acquiring the disease.

By far most work on chemoprevention—including two large randomized controlled trials (RCTs)—has focused on 5α-reductase inhibitors (5ARI). In the PCPT, 18,882 men aged 55 years or older with normal DRE and PSA level <3 ng/mL were randomized to either placebo or finasteride (5 mg/day) (Thompson et al, 2003). Prostate cancer was detected in 18.4% of those on finasteride and 24.4% on placebo, for a 24.8% reduction in prevalence. Cancers of Gleason grades 7 or greater were more common in the finasteride group than in the placebo group (37.0% vs 22.2%). This apparently increased prevalence of high-grade cancers may be artifactual for several reasons, related most importantly to downsizing of benign prostate tissue by the medication and resulting improvement in the receiver operating characteristic curve of prostate biopsy for the *detection* of high-grade cancer (by analogy, one is more likely to find a given needle in a smaller haystack compared to a larger haystack). However, based on the possibility of increased high risk disease, the FDA decided recently not only to decline an expanded label for chemoprevention for 5ARIs but also to add an explicit warning to the labels regarding risk of high-grade prostate cancer (Theoret et al, 2011). Sexual side effects were more common in those receiving finasteride, whereas urinary symptoms were more common in those receiving placebo. A long-term follow-up of PCPT found no difference in survival between the two arms—confirming that treatment effects a ~25% reduction in overdiagnosis with no meaningful increase in oncologic risk (Thompson et al, 2013), and it seems increasingly clear that the FDA made a suboptimal decision in its recommendation.

Another placebo-controlled, randomized trial (the REDUCE study) found a similar 22.8% reduction in incidence of prostate cancer among men 50–75 years of age, with PSA levels at 2.5–10 ng/mL and a prior negative biopsy, who were treated with dutasteride rather than placebo. As in the PCPT, urinary symptoms were significantly ameliorated on the treatment arm, at the expense of sexual side effects among some participants (Andriole et al, 2010).

Uptake of prostate cancer chemoprevention with 5α-reductase inhibitors has been slow since the PCPT was first reported. Although a guideline from the AUA and American Society of Clinical Oncology advises that men at risk be informed of chemoprevention as an option (Kramer et al, 2009), the FDA blackbox warning regarding high-grade disease substantially limited interest among both patients and physicians. No other agents have yet been found to be as promising as 5ARIs. In one notable negative study (the SELECT study), a randomized, placebo-controlled trial of >35,000 men, selenium and vitamin E were shown to be of no benefit for prostate cancer chemoprevention (Lippman et al, 2009); as noted above, selenium supplementation after diagnosis has actually been shown to *increase* disease progression and mortality (Kenfield et al, 2015).

Treatment

A. Localized Disease

1. General considerations—The optimal form of therapy for all stages of prostate cancer remains a subject of perennial debate. Treatment dilemmas persist in the management of localized disease because of the uncertainty surrounding the relative efficacy of various modalities, including surgery, radiation therapy, and active surveillance. Currently, treatment decisions are based on the risk of the tumor, the life expectancy of the patient, the ability of each therapy to ensure disease-free survival and its associated morbidity, and patient and physician preferences. Until recently, there was little information available to ensure that treatment of early-stage disease had an important impact on overall and cancer-specific survival. A well-conducted randomized trial of RP versus surveillance in men with early-stage prostate cancer generally diagnosed before the PSA era was conducted in Scandinavia (Bill-Axelson et al, 2018). With up to 23 years' follow-up, men who underwent RP were less likely to die of prostate cancer (relative risk = 0.55). The advantage to surgery was most apparent in younger patients and those with intermediate-risk disease. A second trial, the Prostate Intervention versus Observation Trial (PIVOT), randomized men between surgery and watchful waiting. The trial, although substantially underpowered because of poor accrual and nontrivial rates of crossover between arms, found no benefit to surgery for low-risk disease, but a substantial survival advantage for men with intermediate-risk disease.

The only randomized controlled trial comparing active local therapies (ie, surgery and radiation therapy) is the ProtecT trial, which also included an active monitoring arm. In the first report from this trial with 10-year follow-up, there was no difference in cancer-specific mortality between surgery and radiation, but the event rate so far was very low, given a cohort of mostly low- and intermediate-risk patients (Hamdy et al, 2016). Of note, the rate of biochemical progression was substantially higher among radiation patients than among surgery patients (Wilt et al, 2017).

Studies of nonrandomized but prospectively accrued cohorts with high-quality data have recently shown, after extensive risk adjustment and various controls for confounding, a mortality benefit for surgery relative to external-beam radiation therapy or hormonal therapy, and for any local therapy (surgery or radiation) relative to hormonal therapy alone (Cooperberg et al, 2010; Zelefsky et al, 2010). The differences seem to be greatest for men with relatively high-risk tumors. While these findings have been somewhat inconsistent across other studies—and while unmeasured confounding is always a highly salient concern in such research—a large meta-analysis recently roughly twofold higher prostate cancer mortality for men treated with external radiation compared to surgery (Wallis et al, 2015).

Despite the ongoing controversies, what is clear is that many men with low-risk disease are candidates for active surveillance (Chen et al, 2016); those with low- to intermediate-risk disease should receive local monotherapy (surgery or radiation), and those with higher-risk disease often need multimodal therapy, either radiation with hormonal therapy or surgery followed selectively by radiation depending on the pathology and early PSA outcomes. These strategies are described in further detail later.

2. Watchful waiting and active surveillance—"Watchful waiting" implies no or minimal monitoring for prostate cancer. Disease-specific mortality at 10 years with such a strategy is low, varying generally between 4% and 15%. However, in further follow-up from 15 to 20 years, a substantial increase in the risk of local and systemic progression and death from prostate cancer may be seen for intermediate- and high-risk cancers (Johansson et al, 2004). The risk of progression is related significantly to cancer grade. The risk of progression is low in those with Gleason grades 2–6 (no pattern 4 or 5), but increases significantly for those with high-grade disease, even among men diagnosed at relatively advanced age (Lu-Yao et al, 2009). Most of the men, in these previously reported series of men managed with watchful waiting, had palpable disease and, therefore, larger, more significant cancer than most of those detected currently based on PSA. In addition, most men were not followed carefully with periodic clinical, radiographic, and laboratory

(PSA) reevaluation. They were treated, usually with androgen deprivation, when symptomatic metastatic disease was detected.

Active surveillance is a more contemporary strategy for prostate cancer and is quite distinct from watchful waiting in several different ways. In active surveillance, men with very well-characterized, early-stage, and low- to intermediate-grade cancer are followed very carefully with serial DRE and PSA assessments, and follow-up TRUS-guided biopsies to ensure stability of the tumor. Cancers are usually treated at the first sign of subclinical progression (Klotz et al, 2015; Tosoian et al, 2015; Welty et al, 2015). Although between 20% and 41% of men on such regimens may require treatment within 5 years of follow-up, treatment at progression appears to be as effective as it would have been if delivered at the time of diagnosis for most men. Optimal surveillance strategies, endpoints for intervention, and exact risks of surveillance have not been well defined as yet. The ProtecT trial found a higher rate of clinical progression among men followed with "active monitoring" with PSA only and no routine biopsies, highlighting the importance for repeat biopsies in a surveillance protocol (Hamdy et al, 2016). Active surveillance is now recommended for most men with low-risk disease and may be considered for some—particularly older men or those with comorbidities—with low-volume Gleason grade group 2 (Chen et al, 2016). Uptake of surveillance in the United States is increasing rapidly, with 40–50% of low-risk cancers in contemporary papers found to be managed with surveillance (Cooperberg et al, 2015; Auffenberg et al, 2017). This rate, while representing great progress, is still too low; the optimal uptake of surveillance for low-risk tumors should likely be closer to 80%, as has been achieved, for example, in Sweden (Loeb et al, 2017).

3. Radical prostatectomy (RP)—The first radical perineal prostatectomy was performed by Hugh Hampton Young in 1904, and Terence Millin first described the radical retropubic approach in 1945. However, the procedure remained unpopular because of frequent complications of incontinence and erectile dysfunction. The rebirth of RP resulted from a better understanding of the surgical anatomy of the pelvis. Description of the anatomy of the dorsal vein complex and prostate apex anatomy resulted in modifications in the surgical technique leading to reduced operative blood loss. In addition, improved visualization made possible a more precise apical dissection, allowing better sparing of the external urethral sphincter and resulting improved continence. Description of the course of the cavernous nerves enabled further modifications of the surgical technique—so-called nerve-sparing techniques—in appropriate cases, resulting in better long-term preservation of erection function (Walsh PC, 2007).

Lymph node dissection should be performed in those at significant risk of lymph node metastases. Such men can be identified using probability tables and nomograms as described earlier. Previously, only limited node dissections were performed harvesting lymph nodes from the obturator fossa. However, results from extended dissections and contemporary PET-CT studies have shown that more than half of lymph node metastases are found outside this region. Therefore, a more extended and meticulous dissection is advised. Some feel that this may not only have diagnostic value but also could have a therapeutic impact in those with limited nodal disease (Allaf et al, 2004; Bader et al, 2003), but this is a highly controversial question. Some men with limited nodal involvement appear to be cured by surgery along, but no high-quality studies have yet demonstrated a survival advantage for lymphadenectomy.

Considerable experience has been gained recently using a laparoscopic approach to RP. This can be performed through an extra- or transperitoneal approach. The advent of the daVinci (Intuitive Surgical, Sunnyvale, CA) surgical robot (a misnomer, as the machine has no autonomous function) has transformed laparoscopic prostatectomy and has been adopted very rapidly in the United States. Laparoscopy reduces blood loss substantially by nature of pneumoperitoneum, shortens the overall recovery time, and in some series reduces hospitalization time. In a meta-analysis comparing retropubic, laparoscopic, and robot-assisted radical prostatectomy, the robotic approach was associated with lower blood loss, fewer transfusions, shorter hospital stays, and lower overall rates of perioperative complications. Assessments of postoperative complications such as readmissions, deep-vein thrombosis, and rectal injury were found to generally favor the robotic approach (Tewari et al, 2012).

Prior meta-analyses of comparative studies and clinical series reported a greater postoperative recovery of urinary continence and potency at 12 months for robot-assisted radical prostatectomy compared to the retropubic approach (Ficarra et al, 2012a, b). Yet the recovery of urinary continence and potency appear for robotic and open surgical approaches do not differ significantly at 24 months' posttreatment (Ficarra et al, 2012b; Cooperberg et al, 2012). However, the robot and associated disposable equipment are expensive, and the cost–benefit relationships must be considered. A lifetime cost–utility analysis of primary treatment modalities for clinically localized prostate cancer showed nonstatistically significant differences between surgical methods, although these costs were lower than radiation therapy across all risk strata (Cooperberg et al, 2012).

The prognosis for patients treated by RP correlates with the pathologic grade and stage of the specimen, and with the PSA response. PSA should fall to undetectable levels within 6 weeks of surgery in most cases. Distant metastases occur in about 85% of patients with positive lymph nodes; some men with limited micrometastatic nodal involvement may be cured by RP and lymphadenectomy, but all men with node involvement should be offered adjuvant androgen deprivation therapy (Messing et al, 2016). A high percentage of patients with seminal vesical involvement at RP, and a smaller proportion of those with extracapsular extension, are likewise destined to distant failure. There are several nomograms and other scoring systems available to help determine prognosis after surgery, similar to those discussed earlier for risk assessment prior to treatment (Coopeerberg et al, 2011; Stephenson et al, 2005).

The management of patients with adverse pathologic features (positive surgical margins, extracapsular extension, and/or seminal vesicle invasion) at RP remains an active topic of discussion. A large multicenter trial sponsored by the Southwest Oncology Group found a nearly 30% relative reduction in metastasis and cancer-specific mortality with 12 years' follow-up for those given adjuvant radiation therapy compared with those observed. However, if all men with these disease features were given adjuvant radiation, many would be overtreated. The problem is that of the men in the control group, fewer than one-third ever received radiation, even after PSA relapse, and radiation was given relatively late in these cases (Thompson et al, 2009). Retrospective studies have shown that administering salvage radiation at relatively low PSA levels results in improved outcomes, with stratification down to a PSA of 0.5 ng/mL. What is unknown is whether there is a benefit to true **adjuvant** radiation—that is, radiation given to a man with adverse pathology but an undetectable PSA—compared with **early salvage**—that is, deferring treatment among those with undetectable PSAs but administering radiation at the first sign of a rising PSA identified with an ultrasensitive assay (ie, with a PSA of >0.01 but <0.1 ng/mL) (Hsu et al, 2015). Relatively good evidence supports earlier rather than later salvage radiation—that is, treating at as low a detectable PSA level as possible (Stephenson et al, 2007).

Morbidity associated with RP can be significant and is in large part related to the skill and experience of the surgeon (Vickers et al, 2011). Immediate intraoperative risks include blood loss, rectal injury, and ureteral injury. Blood loss is more common with the retropubic approach than with the perineal approach because in the former, the dorsal venous complex must be divided. As noted earlier, laparoscopic approaches substantially decrease such bleeding. Rectal injury is rare with the retropubic approach and more common with the perineal approach but usually can be immediately repaired without long-term sequelae. Ureteral injury is rare with any technique. Laparoscopic approaches carry the additional risks of laparoscopic access and insufflation, as well as risks related to transperitoneal access when this approach is used.

Perioperative complications include deep-vein thrombosis, pulmonary embolism, lymphocele formation, and wound infection. Late complications include urinary incontinence and erectile dysfunction. Reported rates of incontinence vary widely depending on the series, how continence is defined and reported, how long after surgery continence is assessed, and other factors. Age, urethral length, and surgeon experience are predictive of continence recovery. The return of continence after surgery may be gradual; many men regain continence by 2–3 months, but recovery can continue up to 1 year. By 24–36 months after surgery, reported continence rates reached 95% (Ficarra 2012b). Most academic series report long-term continence rates of 80–95%; rates from population-based studies are lower.

Preservation of erectile function varies as a function of age, preoperative sexual function, and preservation of one or both neurovascular bundles. If extracapsular extension is present, preservation of the neurovascular bundle may increase the likelihood of a positive margin and disease recurrence. However, it should also be noted that nerve sparing is not a binary decision; the cavernosal nerve is not a single, well-defined structure, but rather a network of small nerve fibers running among the fascial layers surrounding the prostate. On each side, those tissues may be completely spared, partially spared, or widely excised depending on the preoperative findings. Like continence, reported rates of potency preservation vary widely—from 40% to 82% in men younger than 60 years when both nerves are preserved and drops to 20–60% when only one nerve is preserved. For men between the ages of 60 and 69 years, comparable rates are 25–75% with bilateral nerve sparing and 10–50% with unilateral nerve sparing. As with continence, these figures are derived for the most part of academic series and may not be achieved in all practices. Recovery of sexual function generally occurs within 6–24 months following surgery with reported rates of 63–95% by 24 months (Ficarra et al, 2012a). Potency may be improved with early use of PDE5 inhibitors and other, more aggressive approaches to "penile rehabilitation." (See Chapter 39 for more information on erectile dysfunction.)

4. Radiation therapy—external-beam therapy—External beam radiotherapy (XRT) techniques allow the safe delivery of 65–82 Gy to the prostate. Classical XRT techniques depend on bony landmarks to define treatment borders or a single CT slice to define the target volume. These standard XRT techniques generally involve the use of open square or rectangular fields with minimal to no blocking and are characterized by the presence of relatively small boost fields. Often, these XRT techniques fail to provide adequate coverage of the target volume in as many as 20–41% of patients with prostate cancer irradiated, and they are no longer performed in standard US practice.

Improved imaging and use of novel treatment planning (three-dimensional, conformal radiation therapy [3DCRT] and intensity-modulated radiation therapy [IMRT]) allow for better targeting, conforming, or shaping radiation volume more closely around the prostate, and the use of higher doses without exceeding tolerance of surrounding normal tissues. Such radiotherapy has resulted in dramatic reductions in acute and late toxicity of radiation treatment and improved tumor control compared with conventional dose radiotherapy. Doses of ≥72 cGy appear to result in improved biochemical outcomes compared with lower doses. Day-to-day variations in patient/prostate position can be accounted for by daily online CT scanning, transabdominal ultrasound imaging, and insertion of an endorectal balloon or imaging of radiopaque fiducial markers placed before treatment. Whole-pelvis radiation, including regional lymph nodes, especially when combined with androgen deprivation, has demonstrated improved outcomes in those with intermediate and high-risk prostate cancer (Lawton et al, 2007), although this conclusion remains controversial among radiation oncologists (Lawton et al, 2007).

In addition to the use of dose escalation and improved tumor targeting, several investigators have shown that the results of radiation therapy may be improved with the use of neoadjuvant, concurrent, and adjuvant androgen deprivation. Numerous randomized trials have revealed that androgen deprivation improves the outcome of radiation in those with intermediate- or high-risk disease. The use of short-term (3–4 months) neoadjuvant and concurrent androgen deprivation is recommended for those with intermediate-risk disease, whereas those with high-risk disease should receive neoadjuvant, concurrent, and long-term adjuvant (24 months) androgen deprivation (Bolla et al, 2002; Horwitz et al, 2008; Roach et al, 2003).

As with RP, men who receive radiation may experience side effects, especially those related to urinary, bowel, and sexual function. Most such side effects are limited in extent. Although men who undergo surgery are more likely to suffer incontinence, men who undergo radiation are more likely to suffer obstructive or irritative voiding or bowel symptoms (urgency, frequency, diarrhea, hematuria, rectal bleeding, and tenesmus). Although the impact of surgery on sexual function occurs early and may improve with time, the impact of radiation on sexual function may not be seen for 18–24 months. Sexual side effects may be exacerbated with the concurrent use of androgen deprivation, especially if used long term (Wu et al, 2008). Long-term risks, such as urethral stricture, rectourinary fistula, and radiation cystitis, are uncommon but can be quite challenging to manage. There is a doubling of the risk of rectal cancer and bladder cancer starting 10 years after prostate radiation, although the absolute risks of these uncommon tumors remain low (Bhojani et al, 2010).

Given the risk associated with radiation therapy, and concern regarding the efficacy of reduced radiation, there have been ongoing efforts to balance treatment efficacy with posttreatment quality of life and patient-reported outcomes. Studies have explored the impact of variations in radiotherapy such as hypofractionated radiotherapy (dividing the total dose of radiation into larger treatment doses over a shorter time period) and use of CyberKnife (high-dose, targeted stereotactic radiotherapy) on oncologic outcomes and health-related quality of life. For men with low-risk prostate cancer, hypofractionated radiotherapy has been shown to be to conventional radiotherapy with respect to disease-free survival and health-related quality-of-life measures in the bladder, bowel, and sexual domains, with no differences in anxiety and depression (Bruner et al, 2019). Stereotactic body radiotherapy was recently shown to have low rates of severe toxicity and cancer recurrence in a pooled analysis of men with low- and intermediate-risk prostate cancer (Kishan et al, 2018).

It should be reemphasized, however, that most men with low-risk disease should be managed with active surveillance rather than any form of radiation or surgery.

Readers are referred to Chapter 26 for a more detailed discussion of radiation therapy in prostate cancer.

5. Radiation therapy—brachytherapy—With low-dose-rate brachytherapy, a computer guides development of a preplan of a precise dose of radiotherapy to be delivered by TRUS guidance. Implants are permanent (usually iodine-125 or palladium-103) in that the seeds are placed in the prostate, and the radiation dose is delivered over time. In an alternative termed **high-dose-rate (HDR) brachytherapy**, the seeds are loaded into hollow-core catheters and both the seeds (iridium-192) and catheters are removed after a short period of hospitalization and radiation exposure. Permanent implants have a lower dose rate, but a higher total dose delivered compared to temporary implants, which have a higher dose rate, but deliver a lower total dose. External-beam radiation can be given to those with intermediate- and high-risk cancers who receive permanent brachytherapy, and is routinely given to most with high-risk disease who undergo temporary or HDR rate brachytherapy to address pelvic lymph nodes.

As opposed to external-beam radiation, androgen deprivation does not appear to improve the outcomes of men with intermediate disease who are treated with brachytherapy. Androgen deprivation is often used to shrink the prostate prior to brachytherapy to facilitate seed placement, although this does come at the price of additional side effects (Potters et al, 2001). Men with high-risk disease who choose brachytherapy receive external beam radiation and adjuvant androgen deprivation as described for those managed with external-beam techniques alone.

Readers are referred to Chapter 26 for a more detailed discussion of brachytherapy in prostate cancer.

6. Cryosurgery—Cryotherapy has improved in recent years owing to technical innovations, including improved percutaneous techniques, expertise in TRUS, improved cryotechnology, and better understanding of cryobiology.

Freezing of the prostate is carried out by using a multiprobe cryosurgical device. Multiple hollow-core probes are placed transperineally under TRUS guidance. Most surgeons routinely perform two freeze–thaw cycles in all patients, and if the iceball does not adequately extend to the apex of the prostate, the cryoprobes are pulled backward into the apex and additional freeze–thaw cycles are undertaken. The temperature at the edge of the iceball ranges from 0°C to −2°C, while actual cell destruction requires a temperature ranging from −25°C to −50°C. Therefore, actual tissue destruction occurs a few millimeters inside the iceball edge and cannot be monitored precisely by ultrasound imaging. Double freezing creates a larger tissue destruction area and theoretically brings the iceball edge and destruction zone edge closer together. An intraurethral warming device minimizes urethral freezing and subsequent sloughing, thus minimizing risk of severe urinary symptoms and/or retention.

With modern (third-generation) cryoablation systems, severe complications such as rectourethral fistulas are much less common than they once were. However, erectile dysfunction is very common after cryotherapy, more so than after nerve-sparing surgery or radiation therapy, and for this reason cryotherapy has not been widely adopted for primary treatment. However, it is frequently effective for men with biopsy-confirmed locally persistent/recurrent disease after radiation and can serve as an appropriate modality for focal therapy.

7. Focal therapy—Prostate cancer tends to be an infiltrative disease, with cancerous glands interspersed with normal ones, and it is frequently multifocal. Therefore, focal therapy—treating only the tumor while sparing the normal prostate and surrounding structures—is more challenging than for tumors that grow as discrete lesions such as renal cell carcinomas. Multiple modalities are under investigation for this purpose—including limited cryotherapy, high-intensity focused ultrasound (HIFU), interstitial laser therapy, photodynamic therapy, and other techniques. There are several challenges to these approaches, especially the fact that PSA is not a reliable indicator of cancer status after focal ablation, so repeat biopsies after treatment are generally indicated. Ultimately, widespread adoption of focal therapy awaits completing of ongoing prospective trials and validation of better imaging modalities currently under development that will identify—and ideally grade—prostate lesions with greater accuracy.

B. Recurrent Disease

1. Overview—A substantial number of men who are treated with either surgery or radiation for presumed clinically localized prostate cancer will relapse, reflected in a detectable or rising serum PSA after treatment, respectively. Although a persistently detectable serum PSA after surgery is considered a failure, what constitutes biochemical failure after radiation is a matter of some debate. By one count, 152 different definitions have been proposed: 53 after surgery and 99 after radiation therapy. The AUA endorsed the common surgical definition of PSA ≥0.2 ng/mL with a confirmatory value of PSA > 0.2 ng/mL (Cookson et al, 2007).

The American Society for Therapeutic Radiology and Oncology (ASTRO) adopted the definition of three consecutive rises in serum PSA above nadir. However, this has since been modified to improve its specificity by defining failure as a rise of at least 2 ng/mL greater than the nadir level ("Phoenix" definition). It must be recognized that these definitions are neither intended nor able to allow comparisons between surgery and radiation patients, because the surgical definition will identify recurrence about 5 years earlier than the radiation definition (Nielsen et al, 2008). Biochemical failure may have a variable natural history after any kind of initial treatment and may signify localized disease, systemic disease, or a combination of the two. After either form of treatment, an interval to PSA failure of <3–6 years and a posttreatment PSADT of <3 months place a man at increased risk for metastases and subsequent prostate cancer–specific mortality.

2. Following radical prostatectomy—The likelihood of recurrence following RP is related to cancer grade, pathologic stage, margin status, and the extent of extracapsular extension. Cancer recurrence is more common in those with positive surgical margins, established extracapsular extension, seminal vesicle invasion, and high-grade disease. For those patients in whom a detectable PSA level develops after RP, the site of recurrence (local vs distant) can be established with variable certainty, based on the interval from surgery to the detectable PSA concentration, PSADT, and selective use of imaging studies. Indeed, the likelihood of ultimate prostate cancer-specific mortality following PSA recurrence after RP ranges from 1% to 99%, depending on the Gleason score, time to recurrence, and PSADT (Freedland et al, 2005). Patients at low risk (eg, with long interval to recurrence, slow PSA kinetics) and/or those with limited life expectancy may be observed, those with suspected local recurrence (particularly in the setting of positive margins) may benefit from salvage radiation therapy, and those with probable or documented distant disease should receive systemic therapy with androgen deprivation. For men with high risk disease at time of radical prostatectomy, the Decipher test described above has been shown to identify a subset of men with very high risk of early cancer-specific mortality (Cooperberg et al, 2015).

For such men at high risk of recurrence, early identification and salvage therapy can prolong survival and reduce the risk of progression to metastatic disease. Yet it is still unclear who may benefit from salvage treatment and who may die from other causes before metastatic disease can develop. For men with a biochemical recurrence after primary treatment, less than 20% will progress to metastatic disease at 15 years of follow-up (Boorjian et al, 2011). Salvage therapy in this group would be beneficial. In the remaining subset of patients, overdetection of recurrence and overtreatment with salvage therapy will expose individuals to the risks and morbidity of salvage therapy with minimal benefits. One study reported that at least 15.6% of men with biochemical recurrence for 5–10 years after radical prostatectomy would be overdetected and potentially subjected to salvage therapy unnecessarily (Xia et al, 2014).

3. Following radiation therapy—A rising PSA level following definitive radiotherapy is indicative of cancer recurrence. For those who undergo radiation and experience biochemical failure as defined earlier, the site of recurrence may be identified using PSA kinetics, time to failure as noted earlier, prostate biopsies, and selective use of imaging. Up to one-third of patients will experience a "PSA bounce" following radiation (especially brachytherapy), which is defined by a rise in serum PSA followed by a decline. Such patients are not at increased risk of cancer recurrence, and repeat prostate biopsy should be deferred in such patients. Most patients who fail radiation therapy, irrespective of the site of recurrence, usually are managed with androgen deprivation. Those with documented local-only recurrence increasingly are candidates for salvage prostatectomy, cryosurgery, or additional radiation. However, morbidity can be high with these forms of treatment, as is risk of subsequent relapse.

C. Metastatic Disease

1. Initial endocrine therapy—Since death due to prostate cancer almost invariably reflects failure to control metastatic disease, decades of research have concentrated on efforts to improve control of distant disease. Most prostatic carcinomas are initially androgen-dependent, and the vast majority of men with metastatic prostate cancer respond initially to various forms of androgen deprivation. Testosterone, the major circulating androgen, is produced by the Leydig cells in the testes (95%), and a smaller amount is produced by peripheral conversion of other steroids. Free testosterone enters prostate cells and is converted to dihydrotestosterone (DHT), the major intracellular androgen. DHT binds to the cytoplasmic androgen receptor, and the complex moves to the cell nucleus, where it modulates transcription. Androgen deprivation may be induced at several levels along the pituitary–gonadal axis using a variety of methods or agents (Table 21–2).

2. Luteinizing hormone-releasing hormone (LHRH)—Use of a class of drugs (LHRH agonists) has allowed induction of androgen deprivation without orchiectomy or administration of diethylstilbestrol. There are four LHRH agonists currently approved by the FDA for the treatment of prostate cancer: goserelin acetate, triptorelin pamoate, histrelin acetate, and leuprolide acetate. These can be delivered by injection monthly or as depot preparations lasting 1–6 months. A subcutaneous implant that releases leuprolide acetate at a constant rate for 1 year is also available. A second-generation LHRH antagonist (degarelix) has also been released. LHRH antagonists avoid the "flare" phenomenon associated with LHRH agonists, in which serum testosterone concentrations initially increase before falling, but their clinical advantage over LHRH agonists is incompletely defined.

Currently, administration of LHRH agonists is the most common form of primary androgen blockade used in the United States. Orchiectomy, once common, is much less commonly performed today. Like LHRH agonists, estrogens achieve castration by feedback inhibition of the hypothalamic–pituitary axis and, perhaps, by a direct

Table 21–2. Androgen ablation therapy for prostate cancer.

Level	Agent	Dose route	Dose (mg)	Frequency
Pituitary	Diethylstilbestrol Goserelin Leuprolide Histrelin Triptorelin Degarelix	Oral Subcutaneous Intramuscular Subcutaneous Intramuscular Intramuscular	1–3 3.6–10.8 7.5–45 50 11.25–22.5 80	Daily Every 1–3 months Every 1–6 months Annual Every 3–6 months Every month
Adrenal	Ketoconazole Aminoglutethimide Abiraterone	Oral Oral Oral	400 250 1000	Daily Four times a day Daily
Testicle	Orchiectomy			
Prostate cell	Bicalutamide Flutamide Nilutamide Enzalutamide Apalutamide Darolutamide	Oral Oral Oral Oral Oral Oral	50 250 150 160 240 600	Daily Three times a day Daily Daily Daily Twice daily

cytotoxic effect. Although they are effective, their use is limited because of an increased risk of negative cardiovascular and thromboembolic effects. Transdermal estradiol preparations may avoid these risks and are under active investigation.

Because of their rapid onset of action, ketoconazole or abiraterone should be considered in patients with advanced prostate cancer who present with spinal cord compression or disseminated intravascular coagulation. Although testosterone is the major circulating androgen, the adrenal gland secretes the androgens dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione. Prostate cancer cells have also been identified to synthesize androgen directly in the setting of LHRH agonist therapy, thus escaping castration via autocrine pathways. Ketoconazole and abiraterone inhibit androgen biosynthesis throughout the body—in the testes and adrenals and within the tumor cells (de Bono et al, 2011).

Combined androgen blockade can be achieved by combining an androgen receptor antagonist (usually bicalutamide) with the use of an LHRH agonist or orchiectomy. When patients with metastatic prostate cancer are stratified with regard to extent of disease and performance status, those patients with limited disease and a good performance status who are treated with combined androgen blockade (an LHRH agonist and antiandrogen agent) seem to survive longer than those treated with an LHRH agonist alone (Crawford et al, 1989). However, another study comparing the use of an antiandrogen with and without an orchiectomy failed to demonstrate a survival difference between the two arms (Eisenberger et al, 1998). A meta-analysis of monotherapy and complete androgen blockade for the treatment of men with advanced prostate carcinoma suggested that there might be a small survival advantage to complete androgen blockade. This advantage must be balanced against an increased risk of side effects and costs among those on combined therapy (Lukka et al, 2006), often for a number of years.

The timing of initial endocrine therapy in prostate cancer has been an area of intensive debate for many years. Data from the Veterans Administration Cooperative Studies from the 1960s did not demonstrate a clear survival advantage for early intervention with androgen ablation therapy in patients with advanced prostate cancer. However, a randomized study from the Medical Research Council comparing early with delayed endocrine therapy in patients with advanced prostate cancer demonstrated improved survival as well as lower complication rates (cord compression, ureteric obstruction, bladder outlet obstruction, and pathologic fractures) in patients treated with early endocrine therapy (MRCPCWPIG, 1997). Intermittent therapy, compared with continuous therapy, may be associated with improved quality of life as serum testosterone levels may normalize during periods of therapy (Hussain et al, 2013).

In patients who undergo RP and are found to have lymph node involvement, early endocrine therapy has also resulted in a definitive survival advantage (Messing et al, 2006). Most would agree that androgen deprivation should be instituted in all those with metastatic disease, whether symptomatic or not. In addition, there may be an advantage to early therapy in those without radiographic evidence of cancer, but who relapse after initial therapy and are found to have rapid PSADTs as such patients are at great risk of developing metastatic disease early and dying of their disease. However, a precise threshold of PSA or PSA velocity to indicate start of long-term ADT has not been defined.

Androgen deprivation is not without significant side effects, including hot flashes, anemia, loss of libido and sexual function, loss of bone mineral density, increased weight and body fat, and cognitive changes. In addition, increases in total cholesterol, low- and high-density lipoproteins, and serum triglycerides have been reported. Men on androgen deprivation should be monitored for such side effects as treatment for most is readily available. Many men diagnosed with prostate cancer suffer from low bone mineral density, which can be exacerbated with androgen deprivation therapy. Many agents may prevent generalized and localized bone loss, including calcium and vitamin D supplements and, if significant, bisphosphonates or the RANK-ligand inhibitor denosumab. Anemia is usually mild but may be managed with recombinant erythropoietin. Although there are numerous treatment options for men with hot flashes that are especially troublesome, medroxyprogesterone acetate (300–400 mg IM monthly) is an effective treatment with limited side effects.

Ultimately, most prostate cancers will adapt to survive without androgens, at which point they are denoted "castrate-resistant." The armamentarium available for treatment of advanced prostate cancer in this health state is evolving very rapidly. Briefly, interventions now available include the following:

- Cessation of antiandrogen therapy if the patient has been on combined androgen blockade
- Secondary hormonal therapy aimed at the androgen biosynthesis pathway (ketoconazole, abiraterone)
- Second-generation antiandrogens (enzalutamide, apalutamide, darolutamide) that noncompetitively bind the androgen receptor and prevent its nuclear translocation (Potters et al, 2001; Cookson et al, 2007; Nielsen et al, 2007)
- Immunotherapy via administration of autologous dendritic cells primed for recognition of prostatic acid phosphatase (sipuleucel-T)
- Taxane-based chemotherapy (docetaxel, cabazitaxel)
- Bone-directed radionuclide therapy (radium-223)

These agents all have nonoverlapping mechanisms of action, and there is no a priori reason why an individual patient could not receive multiple courses of them. However, no data exist to guide optimal sequencing of these strategies. Moreover, the costs of expensive novel treatments accumulate very quickly, and there is a clear need for much better personalization of treatment based on biomarkers and other predictors of response currently in development. For example, tumors driven by BRCA2 and related mutations may respond particularly well to PARP inhibitors or platinum-based chemotherapy (Pritchard et al, 2016).

Readers are referred to Chapter 25 for a detailed discussion of the therapy for hormone-refractory prostate cancer.

Evaluation and management of prostate cancer has evolved dramatically over the past decade. A growing consensus supports active surveillance for most men with low-risk disease and an aggressive, often multimodal, strategy for those with high-risk disease. The future will see increasing personalization of these management decisions with respect to both timing and intensity of interventions, with the twin goals of further reducing morbidity and mortality from the disease and minimizing the impact on diagnosis and treatment on men's quality of life.

BIBLIOGRAPHY

Ackerstaff E et al: Detection of increased choline compounds with proton nuclear magnetic resonance spectroscopy subsequent to malignant transformation of human prostatic epithelial cells. Cancer Res 2001; 61(9):3599–3603.

Afnan J, Tempany CM: Update on prostate imaging. Urol Clin North Am 2010;37(1):23–25; table of contents (doi: 10.1016/j.ucl.2009.11.009).

Ahmed HU et al: Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. Lancet 2017:1–8 (doi: 10.1016/S0140-6736[16]32401-1).

Allaf ME et al: Anatomical extent of lymph node dissection: Impact on men with clinically localized prostate cancer. J Urol 2004;172 (5 Pt 1):1840–1844.

Andriole GL et al: Effect of dutasteride on the risk of prostate cancer. New Engl J Med 2010;362(13):1192–1202 (doi: 10.1056/NEJMoa0908127).

Andriole GL et al: Mortality results from a randomized prostate-cancer screening trial. New Engl J Med 2009;360(13):1310–1319 (doi: 10.1056/NEJMoa0810696).

Auffenberg GB et al: Practice- vs physician-level variation in use of active surveillance for men with low-risk prostate cancer. JAMA Surg 2017;152(10):978–982 (doi: 10.1001/jamasurg.2017.1586).

Bach-Gansmo T et al: Multisite experience of the safety, detection rate and diagnostic performance of fluciclovine (18F) positron emission tomography/computerized tomography imaging in the staging of biochemically recurrent prostate cancer. J Urol 2017;197(3 Pt 1):676–683 (doi: 10.1016/j.juro.2016.09.117).

Bader P et al: Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? J Urol 2003;169(3):849–854 (doi: 10.1097/01.ju.0000049032.38743.c7).

Bañez LL et al: Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007;298(19):2275–2280 (doi: 10.1001/jama.298.19.2275).

Bhojani N et al: The rate of secondary malignancies after radical prostatectomy versus external beam radiation therapy for localized prostate cancer: A population-based study on 17,845 patients. Int J Radiat Oncol Biol Phys 2010;76(2):342–348 (doi: 10.1016/j.ijrobp.2009.02.011).

Bill-Axelson A et al: Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. New Engl J Med 2018;379(24):2319–2329 (doi: 10.1056/NEJMoa1807801).

Bishoff JT et al: Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 2014;192(2):409–414 (doi: 10.1016/j.juro.2014.02.003).

Bolla M et al: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. Lancet 2002;360(9327):103–108 (doi: 10.1016/S0140-6736[02]09408-4).

Boorjian SA et al: Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: The impact of time from surgery to recurrence. Eur Urol 2011;59(6):893–899 (doi: 10.1016/j.eururo.2011.02.026).

Brajtbord JS et al: The CAPRA score at 10 years: Contemporary perspectives and analysis of supporting studies. Eur Urol 2017;71(5):705–709 (doi: 10.1016/j.eururo.2016.08.065).

Bruner DW et al: Quality of life in patients with low-risk prostate cancer treated with hypofractionated vs conventional radiotherapy: A phase 3 randomized clinical trial. JAMA Oncol February 2019:1–7 (doi: 10.1001/jamaoncol.2018.6752).

Carter HB et al: Early detection of prostate cancer: AUA Guideline. J Urol 2013;190(2):419–426 (doi: 10.1016/j.juro.2013.04.119).

Catalona WJ et al: Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: A prospective multicenter clinical trial. JAMA 1998;279(19):1542–1547.

Chen RC et al: Active surveillance for the management of localized prostate cancer (cancer care Ontario guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol 2016;34(18):2182–2190 (doi: 10.1200/JCO.2015.65.7759).

Cookson MS et al: Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: The American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177(2):540–545 (doi: 10.1016/j.juro.2006.10.097).

Cooperberg MR et al: Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst 2009;101(12):878–887 (doi: 10.1093/jnci/djp122).

Cooperberg MR, Carroll PR: Trends in management for patients with localized prostate cancer, 1990–2013. JAMA 2015;314(1):80–82 (doi: 10.1001/jama.2015.6036).

Cooperberg MR et al: Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol 2015;67(2):326–333 (doi: 10.1016/j.eururo.2014.05.039).

Cooperberg MR et al: The diverse genomic landscape of clinically low-risk prostate cancer. Eur Urol 2018;74(4):444–452 (doi: 10.1016/j.eururo.2018.05.014).

Cooperberg MR et al: The CAPRA-S score. Cancer 2011;117(22):5039–5046 (doi: 10.1002/cncr.26169).

Cooperberg MR et al: The UCSF Cancer of the Prostate Risk Assessment (CAPRA) score: A straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005;173(6):1938–1942 (doi: 10.1097/01.ju.0000158155.33890.e7).

Cooperberg MR et al: Primary treatments for clinically localised prostate cancer: A comprehensive lifetime cost-utility analysis. BJU Int 2012;111(3):437–450 (doi: 10.1111/j.1464-410X.2012.11597.x).

Cooperberg MR et al: Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer 2010;116(22):5226–5234 (doi: 10.1002/cncr.25456).

Cooperberg MR: Prostate cancer risk assessment: Choosing the sharpest tool in the shed. Cancer 2008;113(11):3062–3066 (doi: 10.1002/cncr.23920).

Crawford ED et al: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. New Engl J Med 1989;321(7):419–424 (doi: 10.1056/NEJM198908173210702).

Cullen J et al: A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. Eur Urol 2015;68(1):123–131 (doi: 10.1016/j.eururo.2014.11.030).

Cuzick J et al: Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer 2015;113(3):382–389 (doi: 10.1038/bjc.2015.223).

Cuzick J et al: Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: A retrospective study. Lancet Oncol 2011;12(3): 245–255 (doi: 10.1016/S1470-2045[10]70295-3).

D'Amico AV: Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for clinically localized prostate cancer. JAMA 2000;284(10): 1280–1283 (doi: 10.1001/jama.284.10.1280).

Daouacher G et al: Laparoscopic extended pelvic lymph node (LN) dissection as validation of the performance of [(11) C]-acetate positron emission tomography/computer tomography in the detection of LN metastasis in intermediate- and high-risk prostate cancer. BJU Int 2016;118(1):77–83 (doi: 10.1111/bju.13202).

de Bono JS et al: Abiraterone and increased survival in metastatic prostate cancer. New Engl J Med 2011;364(21):1995–2005 (doi: 10.1056/NEJMoa1014618).

Draisma G et al: Lead time and overdiagnosis in prostate-specific antigen screening: Importance of methods and context. J Natl Cancer Inst 2009;101(6):374–383 (doi: 10.1093/jnci/djp001).

Eisenberger MA et al: Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. New Engl J Med 1998;339(15):1036–1042 (doi: 10.1056/NEJM199810083391504).

Epstein JI et al: A contemporary prostate cancer grading system: A validated alternative to the Gleason Score. Eur Urol 2016;69(3):428–435 (doi: 10.1016/j.eururo.2015.06.046).

Erho N et al: Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS ONE 2013;8(6):e66855 (doi: 10.1371/journal.pone.0066855).

Etzioni R et al: The prostate cancer conundrum revisited. Cancer 2012;118(23):5955–5963 (doi: 10.1002/cncr.27594).

Etzioni R et al: Overdiagnosis due to prostate-specific antigen screening: Lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 2002;94(13):981–990 (doi: 10.1093/jnci/94.13.981).

Ficarra V et al: Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol 2012a;62(3):418–430 (doi: 10.1016/j.eururo.2012.05.046).

Ficarra V et al: Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012b;62(3):405–417 (doi: 10.1016/j.eururo.2012.05.045).

Freedland SJ et al: Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys 2013;86(5):848–853 (doi: 10.1016/j.ijrobp.2013.04.043).

Freedland SJ et al: Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294(4):433–439 (doi: 10.1001/jama.294.4.433).

Giri VN et al: Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 2018;36(4):414–424 (doi: 10.1200/JCO.2017.74.1173).

Greer MD et al: Accuracy and agreement of PIRADSv2 for prostate cancer mpMRI: A multireader study. J Magn Reson Imaging 2017;45(2):579–585 (doi: 10.1002/jmri.25372).

Groskopf J et al: APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem 2006;52(6):1089–1095 (doi: 10.1373/clinchem.2005.063289).

Haese A et al: Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. Eur Urol 2008;54(5):1081–1088 (doi: 10.1016/j.eururo.2008.06.071).

Hamdy FC et al: 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. New Engl J Med 2016;375(15):1415–1424 (doi: 10.1056/NEJMoa1606220).

Haseebuddin M et al: 11C-acetate PET/CT before radical prostatectomy: Nodal staging and treatment failure prediction. J Nucl Med 2013;54(5):699–706 (doi: 10.2967/jnumed.112.111153).

Herlemann A et al: 68Ga-PSMA positron emission tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. Eur Urol 2016;70(4):553–557 (doi: 10.1016/j.eururo.2015.12.051).

Hessels D et al: Detection of TMPRSS2-ERG fusion transcripts and prostate cancer antigen 3 in urinary sediments may improve diagnosis of prostate cancer. Clin Cancer Res 2007;13(17): 5103–5108 (doi: 10.1158/1078-0432.CCR-07-0700).

Horwitz EM et al: Ten-year follow-up of radiation therapy oncology group protocol 92-02: A phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008;26(15):2497–2504 (doi: 10.1200/JCO.2007.14.9021).

Hsu CC et al: Postoperative radiation therapy for patients at high-risk of recurrence after radical prostatectomy: Does timing matter? BJU Int 2015;116(5):713–720 (doi: 10.1111/bju.13043).

Hugosson J et al: Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11(8):725–732 (doi: 10.1016/S1470-2045[10]70146-7).

Hussain M et al: Intermittent versus continuous androgen deprivation in prostate cancer. New Engl J Med 2013;368(14):1314–1325 (doi: 10.1056/NEJMoa1212299).

Jahn JL et al: The high prevalence of undiagnosed prostate cancer at autopsy: Implications for epidemiology and treatment of prostate cancer in the prostate-specific antigen-era. Int J Cancer 2015;137(12):2795–2802 (doi: 10.1002/ijc.29408).

Johansson J-E et al: Natural history of early, localized prostate cancer. JAMA 2004;291(22):2713–2719 (doi: 10.1001/jama.291.22.2713).

Jones JS et al: Saturation prostate biopsy with periprostatic block can be performed in office. J Urol 2002;168(5):2108–2110 (doi: 10.1097/01.ju.0000032367.13879.80).

Karnes RJ et al: Development and validation of a prostate cancer genomic signature that predicts early ADT treatment response following radical prostatectomy. Clin Cancer Res 2018;24(16): 3908–3916 (doi: 10.1158/1078-0432.CCR-17-2745).

Kasivisvanathan V et al: MRI-targeted or standard biopsy for prostate-cancer diagnosis. New Engl J Med 2018;378(19):1767–1777 (doi: 10.1056/NEJMoa1801993).

Kattan MW et al: Counseling men with prostate cancer: A nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol 2003;170(5):1792–1797 (doi: 10.1097/01.ju.0000091806.70171.41).

Kelly SP et al: Trends in the incidence of fatal prostate cancer in the United States by race. Eur Urol 2017;71(2):195–201 (doi: 10.1016/j.eururo.2016.05.011).

Kenfield SA et al: Selenium supplementation and prostate cancer mortality. J Natl Cancer Inst 2015;107(1):360 (doi: 10.1093/jnci/dju360).

Kishan AU et al: Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. JAMA Network Open 2019;2(2):e188006 (doi: 10.1001/jamanetworkopen.2018.8006).

Klein EA et al: A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66(3):550–560 (doi: 10.1016/j.eururo.2014.05.004).

Klotz L et al: Active Surveillance Magnetic Resonance Imaging Study (ASIST): Results of a randomized multicenter prospective trial. Eur Urol 2018:1–10 (doi: 10.1016/j.eururo.2018.06.025).

Klotz L et al: Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33(3):272–277 (doi: 10.1200/JCO.2014.55.1192).

Kramer BS et al: Use of 5α-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Urol 2009;181(4):1642–1657.

Lalonde E et al: Translating a prognostic DNA genomic classifier into the clinic: Retrospective validation in 563 localized prostate tumors. Eur Urol 2017;72(1):22–31 (doi: 10.1016/j.eururo.2016.10.013).

Lange D et al: Bacterial sepsis after prostate biopsy–a new perspective. Urology 2009;74(6):1200–1205 (doi: 10.1016/j.urology.2009.07.1222).

Lawton CA et al: An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: Updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Radiat Oncol Biol 2007;69(3):646–655 (doi: 10.1016/j.ijrobp.2007.04.003).

Leapman MS et al: Application of a prognostic Gleason Grade grouping system to assess distant prostate cancer outcomes. Eur Urol 2017;71(5):750–759 (doi: 10.1016/j.eururo.2016.11.032).

Leapman MS et al: Clinical utility of biomarkers in localized prostate cancer. Curr Oncol Rep April 2016:1–10 (doi: 10.1007/s11912-016-0513-1).

Lin DW et al: Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. Urol Oncol 2018;36(6):310.e7–310.e13 (doi: 10.1016/j.urolonc.2018.03.011).

Lippman SM et al: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301(1):39–51 (doi: 10.1001/jama.2008.864).

Loeb S et al: Uptake of active surveillance for very-low-risk prostate cancer in Sweden. JAMA Oncol 2017;3(10):1393–1396 (doi: 10.1001/jamaoncol.2016.3600).

Loeb S, Ross AE: Genomic testing for localized prostate cancer: Where do we go from here? Curr Opin Urol 2017;27(5):495–499 (doi: 10.1097/MOU.0000000000000419).

Lughezzani G et al: Head-to-head comparison of the three most commonly used preoperative models for prediction of biochemical recurrence after radical prostatectomy. Eur Urol 2010;57(4):562–568 (doi: 10.1016/j.eururo.2009.12.003).

Lukka H et al: Maximal androgen blockade for the treatment of metastatic prostate cancer—a systematic review. Curr Oncol 2006;13(3):81–93.

Lu-Yao GL et al: Outcomes of localized prostate cancer following conservative management. JAMA 2009;302(11):1202–1209 (doi: 10.1001/jama.2009.1348).

Makarov DV et al: Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology 2007;69(6):1095–1101 (doi: 10.1016/j.urology.2007.03.042).

McKiernan J et al: A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. JAMA Oncol 2016;2(7):882–889 (doi: 10.1001/jamaoncol.2016.0097).

Meng MV et al: The utility of apical anterior horn biopsies in prostate cancer detection. Urol Oncol 2003;21(5):361–365.

Messing EM et al: Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7(6):472–479 (doi: 10.1016/S1470-2045[06]70700-8).

MRCPWPIG (The Medical Research Council Prostate Cancer Working Party Investigators Group): Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol 1997;79(2):235–246.

Narod SA et al: Fusion in the ETS gene family and prostate cancer. Br J Cancer 2008;99(6):847–851 (doi: 10.1038/sj.bjc.6604558).

Nguyen PL et al: Utilization of biopsy-based genomic classifier to predict distant metastasis after definitive radiation and short-course ADT for intermediate and high-risk prostate cancer. Prost Cancer Prostat Dis January 2017 (doi: 10.1038/pcan.2016.58).

Nielsen ME et al: Is it possible to compare PSA recurrence-free survival after surgery and radiotherapy using revised ASTRO criterion–"nadir + 2"? Urology 2008;72(2):389–293; discussion 394–395 (doi: 10.1016/j.urology.2007.10.053).

Nordström T et al: Comparison between the Four-kallikrein Panel and Prostate Health Index for predicting prostate cancer. Eur Urol 2015;68(1):139–146 (doi: 10.1016/j.eururo.2014.08.010).

Odewole OA et al: Recurrent prostate cancer detection with anti-3-[18F] FACBC PET/CT: Comparison with CT. Eur J Nucl Med Mol Imaging 2016;43(10):1773–1783 (doi: 10.1007/s00259-016-3383-8).

Okudaira H et al: Accumulation of trans-1-amino-3-[(18)F]fluorocyclobutanecarboxylic acid in prostate cancer due to androgen-induced expression of amino acid transporters. Mol Imaging Biol 2014;16(6):756–764 (doi: 10.1007/s11307-014-0756-x).

Palvolgyi R et al: Bone scan overuse in staging of prostate cancer: An analysis of a Veterans Affairs cohort. Urology 2011;77(6):1330–1336 (doi: 10.1016/j.urology.2010.12.083).

Pinsky PF et al: Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123(4):592–599 (doi: 10.1002/cncr.30474).

Potters L et al: Potency after permanent prostate brachytherapy for localized prostate cancer. Radiat Oncol Biol 2001;50(5):1235–1242.

Poulsen MH et al: Spine metastases in prostate cancer: Comparison of technetium-99m-MDP whole-body bone scintigraphy, [18F] choline positron emission tomography(PET)/computed tomography (CT) and [18F]NaF PET/CT. BJU Int 2014;114(6):818–823 (doi: 10.1111/bju.12599).

Preston MA et al: Baseline prostate-specific antigen level in midlife and aggressive prostate cancer in black men. Eur Urol 2018:1–9 (doi: 10.1016/j.eururo.2018.08.032).

Pritchard CC et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. New Engl J Med 2016;375(5):443–453 (doi: 10.1056/NEJMoa1603144).

Quigley DA et al: Genomic hallmarks and structural variation in metastatic prostate cancer. Cell 2018;174(3):758–769, e759 (doi: 10.1016/j.cell.2018.06.039).

Reese AC et al: Minimal impact of clinical stage on prostate cancer prognosis among contemporary patients with clinically localized disease. J Urol 2010;184(1):114–119 (doi: 10.1016/j.juro.2010.03.025).

Rider JR et al: Ejaculation frequency and risk of prostate cancer: Updated results with an additional decade of follow-up. Eur Urol 2016;70(6):974–982 (doi: 10.1016/j.eururo.2016.03.027).

Roach M et al: Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003;21(10):1904–1911 (doi: 10.1200/JCO.2003.05.004).

Ross AE et al: Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. Eur Urol 2016;69(1):157–165 (doi: 10.1016/j.eururo.2015.05.042).

Schiavina R et al: Preoperative staging with 11C-choline PET/CT is adequately accurate in patients with very high-risk prostate cancer. Clin Genitourin Cancer 2018;16(4):305–312, e1 (doi: 10.1016/j.clgc.2018.05.010).

Schroder FH et al: Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384(9959):2027–2035 (doi: 10.1016/S0140-6736[14]60525-0).

Shariat SF et al: An updated catalog of prostate cancer predictive tools. Cancer 2008;113(11):3075–3099 (doi: 10.1002/cncr.23908).

Siegel RL et al: Cancer statistics, 2019. CA Cancer J Clin 2019;69(1):734 (doi: 10.3322/caac.21551).

Sonn GA et al: Prostate magnetic resonance imaging interpretation varies substantially across radiologists. Eur Urol Focus December 2017 (doi: 10.1016/j.euf.2017.11.010).

Stephenson AJ et al: Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2005;23(28):7005–7012 (doi: 10.1200/JCO.2005.01.867).

Stephenson AJ et al: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25(15):2035–2041 (doi: 10.1200/JCO.2006.08.9607).

Tewari A et al: Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: A systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. Eur Urol 2012;62(1):1–15 (doi: 10.1016/j.eururo.2012.02.029).

Theoret MR et al: The risks and benefits of 5α-reductase inhibitors for prostate-cancer prevention. New Engl J Med 2011;365(2):97–99 (doi: 10.1056/NEJMp1106783).

Thompson I et al: Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol 2007;177(6):2106–2131 (doi: 10.1016/j.juro.2007.03.003).

Thompson IM et al: Long-term survival of participants in the prostate cancer prevention trial. New Engl J Med 2013;369(7):603–610 (doi: 10.1056/NEJMoa1215932).

Thompson IM et al: Prevention of prostate cancer with finasteride: US/European perspective. Eur Urol 2003;44(6):650–655.

Thompson IM et al: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term followup of a randomized clinical trial. J Urol 2009;181(3):956–962 (doi: 10.1016/j.juro.2008.11.032).

Tosoian JJ et al: Prognostic utility of biopsy-derived cell cycle progression score in patients with National Comprehensive Cancer Network low-risk prostate cancer undergoing radical prostatectomy: Implications for treatment guidance. BJU Int 2017;120(6):808–814 (doi: 10.1111/bju.13911).

Tosoian JJ et al: Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33(30):3379–3385 (doi: 10.1200/JCO.2015.62.5764).

Tran GN et al: Magnetic resonance imaging-ultrasound fusion biopsy during prostate cancer active surveillance. Eur Urol 2016:1–7 (doi: 10.1016/j.eururo.2016.08.023).

Tsodikov A et al: Is prostate cancer different in black men? Answers from 3 natural history models. Cancer 2017;123(12):2312–2319 (doi: 10.1002/cncr.30687).

Tsodikov A et al: Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med 2017;167(7):449 (doi: 10.7326/M16-2586).

Van Neste L et al: Detection of high-grade prostate cancer using a urinary molecular biomarker-based risk score. Eur Urol 2016:1–9 (doi: 10.1016/j.eururo.2016.04.012).

Verma S et al: Prostate MRI and 3D MR spectroscopy: How we do it. Am J Roentgenol 2010;194(6):1414–1426 (doi: 10.2214/AJR.10.4312).

Vickers A et al: It ain't what you do, it's the way you do it: Five golden rules for transforming prostate-specific antigen screening. Eur Urol 2014a;66(2):188–190 (doi: 10.1016/j.eururo.2013.12.049).

Vickers A et al: Cancer control and functional outcomes after radical prostatectomy as markers of surgical quality: Analysis of heterogeneity between surgeons at a single cancer center. Eur Urol 2011;59(3):317–322 (doi: 10.1016/j.eururo.2010.10.045).

Vickers AJ et al: A simple schema for informed decision making about prostate cancer screening. Ann Intern Med 2014b;161(6):441–442 (doi: 10.7326/M14-0151).

Vickers AJ et al: An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. J Natl Cancer Inst 2011;103(6):462–469 (doi: 10.1093/jnci/djr028).

Vickers AJ et al: Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: Case-control study. Br Med J 2013;346(5):f2023 (doi: 10.1136/bmj.f2023).

Vidal AC, Freedland SJ: Obesity and prostate cancer: A focused update on active surveillance, race, and molecular subtyping. Eur Urol 2017;72(1):78–83 (doi: 10.1016/j.eururo.2016.10.011).

Vinsensia M et al: 68Ga-PSMA PET/CT and volumetric morphology of PET-positive lymph nodes stratified by tumor differentiation of prostate cancer. J Nucl Med 2017;58(12):1949–1955 (doi: 10.2967/jnumed.116.185033).

Wallis CJD et al: Surgery versus radiotherapy for clinically-localized prostate cancer: A systematic review and meta-analysis. Eur Urol 2016;70(1):21–30 (doi: 10.1016/j.eururo.2015.11.010).

Wegelin O et al: The FUTURE Trial: A multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. Eur Urol December 2018 (doi: 10.1016/j.eururo.2018.11.040).

Wegelin O et al: Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: A systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? Eur Urol 2017;71(4):517–531 (doi: 10.1016/j.eururo.2016.07.041).

Wei JT et al: Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol 2014;32(36):4066–4072 (doi: 10.1200/JCO.2013.52.8505).

Welty CJ et al: Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J Urol 2015;193(3):807–811 (doi: 10.1016/j.juro.2014.09.094).

Wilt TJ et al: Follow-up of prostatectomy versus observation for early prostate cancer. New Engl J Med 2017;377(2):132–142 (doi: 10.1056/NEJMoa1615869).

Wu AK et al: Health related quality of life in patients treated with multimodal therapy for prostate cancer. J Urol 2008;180(6):2415–2422; discussion 2422 (doi: 10.1016/j.juro.2008.08.015).

Xia J et al: Overdetection of recurrence after radical prostatectomy: Estimates based on patient and tumor characteristics. Clin Cancer Res 2014;20(20):5302–5310 (doi: 10.1158/1078-0432.CCR-13-3366).

Yoshii Y et al: Acetate/acetyl-CoA metabolism associated with cancer fatty acid synthesis: Overview and application. Cancer Lett 2015;356(2 Pt A):211–216 (doi: 10.1016/j.canlet.2014.02.019).

Zelefsky MJ et al: Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: A comparison of clinical cohorts adjusted for case mix. J Clin Oncol 2010;28(9):1508–1513 (doi: 10.1200/JCO.2009.22.2265).

Zhang L et al: A meta-analysis of use of Prostate Imaging Reporting and Data System Version 2 (PI-RADS V2) with multiparametric MR imaging for the detection of prostate cancer. Eur Radiol 2017;27(12):5204–5214 (doi: 10.1007/s00330-017-4843-7).

Zhao SG et al: Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. JAMA Oncol 2017;3(12):1663–1610 (doi: 10.1001/jamaoncol.2017.0751).

Zhao SG et al: Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: A matched, retrospective analysis. Lancet Oncol 2016;17(11):1612–1620 (doi: 10.1016/S1470-2045[16]30491-0).

Genital Tumors

22

Sima P. Porten, MD, MPH; & Joseph C. Presti, Jr., MD

TUMORS OF THE TESTIS

GERM CELL TUMORS OF THE TESTIS

Epidemiology and Risk Factors

Malignant tumors of the testis are rare, with approximately five new cases per 100,000 males reported in the United States each year. Of all primary testicular tumors, 95% are germ cell tumors (seminoma and nonseminoma), while the remainder are sex cord or stromal tumors (Leydig cell, Sertoli cell, gonadoblastoma). The lifetime probability of developing testicular cancer is 0.2% for a Caucasian male in the United States. Survival of patients with testicular cancer has improved dramatically in recent years, reflecting the development and refinement of effective combination chemotherapy. Of the 8480 new cases of testicular cancer in the United States in 2010, only 350 deaths are expected.

The incidence of testicular cancer shows marked variation among different countries, races, and socioeconomic classes. Scandinavian countries report up to 6.7 new cases per 100,000 males annually; Japan reports 0.8 per 100,000 males. In the United States, the incidence of testicular cancer in African-Americans is approximately one-fourth that in Caucasians. Within a given race, individuals in the higher socioeconomic classes have approximately twice the incidence of those in the lower classes.

Testicular cancer is slightly more common on the right side than on the left, which parallels the increased incidence of cryptorchidism on the right side. Of primary testicular tumors, 1–2% are bilateral, and about 50% of these tumors occur in men with a history of unilateral or bilateral cryptorchidism. Primary bilateral tumors of the testis may occur synchronously or asynchronously but tend to be of the same histologic type. Seminoma is the most common germ cell tumor in bilateral *primary* testicular tumors, while malignant lymphoma is the most common bilateral tumor of the testis.

Although the cause of testicular cancer is unknown, both congenital and acquired factors have been associated with tumor development. The strongest association has been with the cryptorchid testis. Approximately 7–10% of testicular tumors develop in patients who have a history of cryptorchidism; seminoma is the most common form of tumor that these patients have. However, 5–10% of testicular tumors occur in the contralateral, normally descended testis. The relative risk of malignancy is highest for the intra-abdominal testis (1 in 20) and is significantly lower for the inguinal testis (1 in 80). Placement of the cryptorchid testis into the scrotum (orchiopexy) lowers the risk of malignancy if it is performed prior to the age of 13 years (Pettersson et al, 2007). Intratubular germ cell neoplasia (ITGCN) is another major risk factor and approximately half of men with ITGCN will develop a germ cell tumor in 5 years.

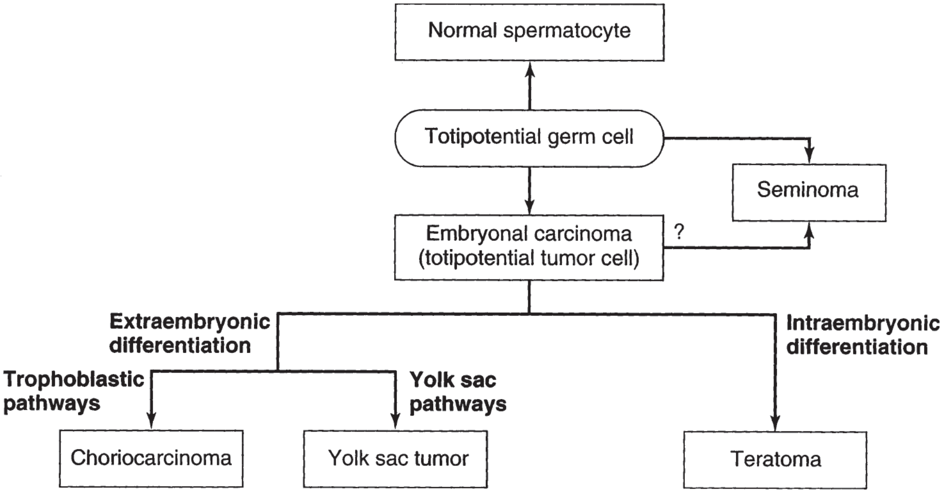
Exogenous estrogen administration to the mother during pregnancy has been associated with an increased relative risk for testicular tumors in the fetus, ranging from 2.8 to 5.3 over the expected incidence. Other acquired factors such as trauma and infection-related testicular atrophy have been associated with testicular tumors; however, a causal relationship has not been established.

Classification

Numerous classification systems have been proposed for germ cell tumors of the testis. Classification by histologic type proves to be the most useful with respect to treatment. The two major divisions are seminoma and nonseminomatous germ cell tumors (NSGCTs), which include embryonal, teratoma, choriocarcinoma, and mixed tumors.

Tumorigenic Hypothesis for Germ Cell Tumor Development

During embryonal development, the totipotential germ cells can travel down normal differentiation pathways and



▲ **Figure 22–1.** Tumorigenic model for germ cell tumors of the testis.

become spermatocytes. However, if these totipotential germ cells travel down abnormal developmental pathways, seminoma or embryonal carcinomas (totipotential tumor cells) develop. If the embryonal cells undergo further differentiation along intraembryonic pathways, teratoma will result. If the embryonal cells undergo further differentiation along extraembryonic pathways, either choriocarcinoma or yolk sac tumors are formed (Figure 22–1). This model helps to explain why specific histologic patterns of testicular tumors produce certain tumor markers. Note that yolk sac tumors produce α-fetoprotein (AFP) just as the yolk sac produces AFP in normal development. Likewise, choriocarcinoma produces human chorionic gonadotropin (hCG) just as the normal placenta produces hCG.

▶ Pathology

A. Seminoma

Three histologic subtypes of pure seminoma have been described. However, stage for stage, there is no prognostic significance to any of these subtypes. Classic seminoma accounts for 85% of all seminomas and is most common in the fourth decade of life. Grossly (macroscopically), coalescing gray nodules are observed. Microscopically, monotonous sheets of large cells with clear cytoplasm and densely staining nuclei are seen. It is noteworthy that syncytiotrophoblastic elements are seen in approximately 15% of cases, an incidence that corresponds approximately to the incidence of hCG production in seminomas.

Anaplastic seminoma accounts for 5–10% of all seminomas. Diagnosis requires the presence of three or more mitoses per high-power field, and the cells demonstrate a higher degree of nuclear pleomorphism than the classic types. Anaplastic seminoma tends to present at a higher stage than the classic variety. When stage is taken into consideration, however, this subtype does not convey a worse prognosis.

Spermatocytic seminoma accounts for 1% of all seminomas and has been renamed as "spermatocytic tumor" in the 2016 WHO classification. Microscopically, cells vary in size and are characterized by densely staining cytoplasm and round nuclei that contain condensed chromatin. More than half of the patients with spermatocytic seminoma are older than 50 years.

B. Nonseminoma Germ Cell Tumors

1. Embryonal cell carcinoma and yolk sac—Two variants of embryonal cell carcinoma are common: the adult type and the infantile type or yolk sac tumor (also called endodermal sinus tumor). The histologic structure of the adult variant demonstrates marked pleomorphism and indistinct cellular borders. Mitotic figures and giant cells are common. Cells may be arranged in sheets, cords, glands, or papillary structures. Extensive hemorrhage and necrosis may be observed grossly.

The infantile variant, or yolk sac tumor, is the most common testicular tumor of infants and children. When seen in adults, it usually occurs in mixed histologic types (40%) and possibly is responsible for AFP production in these tumors. Microscopically, cells demonstrate vacuolated cytoplasm secondary to fat and glycogen deposition and are arranged in a loose network with large intervening cystic spaces. Embryoid bodies are commonly seen and resemble 1–2-week-old embryos consisting of a cavity surrounded by syncytio- and cytotrophoblasts.

2. Teratoma—Teratomas may be seen in both children and adults and represent 5% of GCTs. They contain more than one germ cell layer in various stages of maturation and differentiation. Grossly, the tumor appears lobulated and contains variable-sized cysts filled with gelatinous or mucinous material. A mature teratoma may contain elements resembling benign structures derived from ectoderm, mesoderm, and endoderm, while an immature teratoma consists of undifferentiated primitive tissue. In contrast to its ovarian counterpart, the mature teratoma of the testis does not attain the same degree of differentiation as the ovarian teratoma. Microscopically, ectoderm may be represented by squamous epithelium or neural tissue; endoderm may be represented by intestinal, pancreatic, or respiratory tissue; and mesoderm may be represented by smooth or skeletal muscle, cartilage, or bone.

3. Choriocarcinoma—Pure choriocarcinoma is rare (representing only 1% of GCTs, 10% mixed tumors). Lesions tend to be small within the testis and usually demonstrate central hemorrhage on gross inspection. Microscopically, syncytio- and cytotrophoblasts must be visualized. The syncytial elements are typically large, multinucleated cells with vacuolated, eosinophilic cytoplasm; the nuclei are large, hyperchromatic, and irregular. Cytotrophoblasts are uniform cells with distinct cell borders, clear cytoplasm, and a single nucleus.

Clinically, choriocarcinomas behave in an aggressive fashion characterized by early hematogenous spread. Paradoxically, small intratesticular lesions can be associated with widespread metastatic disease.

4. Mixed cell type—Within the category of mixed cell types, most (up to 25% of all testicular tumors) are teratocarcinomas, which are a combination of teratoma and embryonal cell carcinoma. Up to 6% of all testicular tumors are of mixed cell type; seminoma is one of the components. Treatment for these mixtures of seminoma and NSGCT is similar to that for NSGCT alone.

C. Carcinoma In Situ

In a series of 250 patients with unilateral testicular cancer, Berthelsen et al (1982) demonstrated the presence of carcinoma in situ (CIS) in 13 (5.2%) of the contralateral testes. This is approximately twice the overall incidence of bilateral testicular cancer. The presence of contralateral atrophy or ultrasonographic microlithiasis in patients with testicular tumors warrants contralateral biopsy. If diagnosed, CIS is usually treated by external beam radiation therapy.

Patterns of Metastatic Spread

With the exception of choriocarcinoma, which demonstrates early hematogenous spread, germ cell tumors of the testis typically spread in a stepwise lymphatic fashion. Lymph nodes of the testis extend from T1 to L4 but are concentrated at the level of the renal hilum because of their common embryologic origin with the kidney. The primary landing site for the right testis is the interaortocaval area at the level of the right renal hilum. Stepwise spread, in order, is to the precaval, preaortic, paracaval, right common iliac, and right external iliac lymph nodes. The primary landing site for the left testis is the para-aortic area at the level of the left renal hilum. Stepwise spread, in order, is to the preaortic, left common iliac, and left external iliac lymph nodes. In the absence of disease on the left side, no crossover metastases to the right side have ever been identified. However, right-to-left crossover metastases are common. These observations have resulted in modified surgical dissections to preserve ejaculation in selected patients (see section titled "Treatment").

Certain factors may alter the primary drainage of a testis neoplasm. Invasion of the epididymis or spermatic cord may allow spread to the distal external iliac and obturator lymph nodes. Scrotal violation or invasion of the tunica albuginea may result in inguinal metastases. Although the retroperitoneum is the most commonly involved site in metastatic disease, visceral metastases may be seen in advanced disease. The sites involved in decreasing frequency include lung, liver, brain, bone, kidney, adrenal, gastrointestinal tract, and spleen. As mentioned previously, choriocarcinoma is the exception to the rule and is characterized by early hematogenous spread, especially to the lung. Choriocarcinoma has also a predilection for unusual sites of metastasis such as the spleen.

Clinical Staging

Many clinical staging systems have been proposed for testicular cancer. However, most are variations of the original system proposed by Boden and Gibb (1951). In this system, a stage A lesion was confined to the testis, stage B demonstrated regional lymph node spread, and stage C was spread beyond retroperitoneal lymph nodes. Numerous clinical staging systems have also been suggested for seminoma. A stage I lesion is confined to the testis. Stage II has retroperitoneal nodal involvement (IIA is <2 cm, IIB is 2–5 cm, and IIC is >5 cm). Stage III has supradiaphragmatic nodal involvement or visceral involvement. The TNM classification of American Joint Committee (2010) has attempted to standardize clinical stages as shown in Table 22–1.

Clinical Findings

A. Symptoms

The most common symptom of testicular cancer is a painless enlargement of the testis. Enlargement is usually gradual, and a sensation of testicular heaviness is not unusual. The typical delay in treatment from initial recognition of the lesion by the patient to definitive therapy (orchiectomy) ranges from 3 to 6 months. The length of delay correlates with the incidence of metastases. The importance of patient awareness and self-examination is apparent. Acute testicular pain is seen in approximately 10% of cases and may be the result of intratesticular hemorrhage or infarction.

Table 22–1. TNM classification of tumors of the testis.

Pathological T (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia *in situ*
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
pT1a*	Tumor smaller than 3 cm in size
pT1b*	Tumor 3 cm or larger in size
pT2	Tumor limited to testis (including rete testis invasion) with lymphovascular invasion OR Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT3	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion

*Subclassification of pT1 applies only to pure seminoma.

Pathological N (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastases
M1	Distant metastases
M1a	Non-retroperitoneal nodal or pulmonary metastases
M1b	Non-pulmonary visceral metastases

Definition of Serum Markers (S)

S Category	S Criteria
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × N* *and* hCG (mIU/mL) < 5,000 *and* AFP (ng/mL) < 1,000
S2	LDH 1.5–10 × N* *or* hCG (mIU/mL) 5,000 – 50,000 *or* AFP (ng/mL) 1,000–10,000
S3	LDH > 10 × N* *or* hCG (mIU/mL) > 50,000 *or* AFP (ng/mL) > 10,000

*N indicates the upper limit of normal for the LDH assay.

Used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) *AJCC Cancer Staging Manual*, 8th Ed. Springer New York, 2017.

Approximately 10% of patients present with symptoms related to metastatic disease. Back pain (retroperitoneal metastases involving nerve roots) is the most common symptom. Other symptoms include cough or dyspnea (pulmonary metastases); anorexia, nausea, or vomiting (retroduodenal metastases); bone pain (skeletal metastases); and lower extremity swelling (vena caval obstruction).

Approximately 10% of patients are asymptomatic at presentation, and the tumor may be detected incidentally following trauma, or it may be detected by the patient's sexual partner.

B. Signs

A testicular mass or diffuse enlargement is found in most cases. The mass is typically firm and nontender, and the epididymis should be easily separable from it. A hydrocele may accompany the testicular tumor and help to camouflage it. Transillumination of the scrotum can help to distinguish between these entities.

Palpation of the abdomen may reveal bulky retroperitoneal disease; assessment of supraclavicular, scalene, and inguinal nodes should be performed. Gynecomastia is present in 5% of all germ cell tumors but may be present in 30–50% of Sertoli and Leydig cell tumors. Its cause seems to be related to multiple complex hormonal interactions involving testosterone, estrone, estradiol, prolactin, and hCG. Hemoptysis may be seen in advanced pulmonary disease.

C. Laboratory Findings and Tumor Markers

Anemia may be detected in advanced disease. Liver function tests may be elevated in the presence of hepatic metastases. Renal function may be diminished (elevated serum creatinine) if ureteral obstruction secondary to bulky retroperitoneal disease is present. The assessment of renal function (creatinine clearance) is mandatory in patients with advanced disease who require chemotherapy.

Several biochemical markers are of importance in the diagnosis and management of testicular carcinoma, including AFP, hCG, and lactic acid dehydrogenase (LDH). AFP is a glycoprotein with a molecular mass of 70,000 Da and a half-life of 5–7 days. Although present in fetal serum in high levels, beyond the age of 1 year, it is present only in trace amounts but can be elevated in patients with liver disease and gastrointestinal tumors. While present to varying degrees in many NSGCTs (Table 22–2), it is never found in seminomas.

Human chorionic gonadotropin (hCG) is a glycoprotein with a molecular mass of 38,000 Da and a half-life of 24-36 hours. It is composed of two subunits: α and β. The α subunit is similar to the α subunits of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH). The β subunit conveys the activity to each of these hormones and allows for a highly sensitive and specific radioimmunoassay in the determination of hCG levels. A normal man should not have significant levels of β-hCG;

Table 22–2. Incidence of elevated tumor markers by histologic type in testis cancer.

	hCG (%)	AFP (%)
Seminoma	7	0
Teratoma	25	38
Teratocarcinoma	57	64
Embryonal	60	70
Choriocarcinoma	100	0

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin.

however, it can be slightly elevated from heavy marijuana use. While more commonly elevated in NSGCTs, hCG levels may be elevated in up to 7% of seminomas.

Lactic acid dehydrogenase (LDH) is a cellular enzyme with a molecular mass of 134,000 Da that has five isoenzymes; it is normally found in muscle (smooth, cardiac, and skeletal), liver, kidney, and brain. Elevation of total serum LDH, particularly isoenzyme I, was shown to correlate with tumor burden in NSGCTs. LDH may also be elevated in seminoma and has a half-life of 24 hours.

Other markers have been described for testis cancer, including placental alkaline phosphatase (PLAP) and γ-glutamyl transpeptidase (GGT). These markers, however, have not contributed as much to the management of patients as those mentioned previously.

D. Imaging

The primary testicular tumor can be rapidly and accurately assessed by scrotal ultrasonography. This technique can determine whether the mass is truly intratesticular, can be used to distinguish the tumor from epididymal pathology, and may also facilitate testicular examination in the presence of a hydrocele.

Once the diagnosis of testicular cancer has been established by inguinal orchiectomy, careful clinical staging of disease is mandatory. Chest radiographs (posteroanterior and lateral) and computed tomography (CT scan) of the abdomen and pelvis are used to assess the two most common sites of metastatic spread, namely, the lungs and retroperitoneum. The use of magnetic resonance imaging (MRI) is increasing in lieu of CT scans, due to concern of radiation exposure, particularly when surveillance is used as a primary management strategy. The role of CT scanning of the chest remains controversial because of its decreased specificity and the fact that routine chest x-rays (CXRs) can detect 85–90% of pulmonary metastases. Pedal lymphangiography (LAG) is rarely used because of its invasiveness and low specificity.

▶ Differential Diagnosis

An incorrect diagnosis is made at the initial examination in up to 25% of patients with testicular tumors and may result in delay in treatment or a suboptimal surgical approach (scrotal incision) for exploration. Epididymitis or epididymitis-related orchitis is the most common misdiagnosis in patients with testicular cancer. Early epididymitis should reveal an enlarged, tender epididymis that is clearly separable from the testis. In advanced stages, the inflammation may spread to the testes and result in an enlarged, tender, and indurated testis and epididymis. A history of acute onset of symptoms including fever, urethral discharge, and irritative voiding symptoms may make the diagnosis of epididymitis more likely. Ultrasonography may identify the enlarged epididymis as the cause of the scrotal mass.

Hydrocele is the second most common misdiagnosis. Transillumination of the scrotum may readily distinguish between a translucent, fluid-filled hydrocele, and a solid testicular tumor. Since 5–10% of testicular tumors may be associated with hydroceles, if the testes cannot be adequately examined, a scrotal ultrasound examination is mandatory. Aspiration of the hydrocele should be avoided because positive cytologic results have been reported in hydroceles associated with testicular tumors.

Other diagnoses to be considered include spermatocele, a cystic mass most commonly found extending from the head of the epididymis; hematocele, associated with trauma; granulomatous orchitis, most commonly resulting from tuberculosis and associated with beading of the vas deferens; and varicocele, which is engorgement of the pampiniform plexus of veins in the spermatic cord and should disappear when the patient is in the supine position.

Although most intratesticular masses are malignant, one benign lesion, an epidermoid cyst, may be seen on rare occasions. Usually, these cysts are very small benign nodules located just underneath the tunica albuginea; however, on occasion, they can be large. The diagnosis is usually made following inguinal orchiectomy; as frozen sections, the larger lesions are often difficult to distinguish from teratoma.

▶ Treatment

Inguinal exploration with cross-clamping of the spermatic cord vasculature and delivery of the testis into the field is the mainstay of exploration for a possible testicular tumor. If cancer cannot be excluded by examination of the testis, radical orchiectomy is warranted. Partial orchiectomy for testis sparing can be considered in the case of a small tumor, solitary testis, or suspicion for benign pathology. Scrotal approaches and open testicular biopsies should be avoided. Further therapy depends on the histologic characteristics of the tumor as well as the clinical stage.

A. Low-Stage Seminoma

Options for management after radical orchiectomy for stage I seminoma are surveillance, radiotherapy, and carboplatin chemotherapy. Low-stage seminoma has a very favorable survival rate of 99% irrespective of management strategy used, and 80% of patients with stage I seminoma are cured with radical orchiectomy alone. Because both radiation and chemotherapy are associated with some morbidity and secondary malignancy risk, surveillance is the preferred option in stage I seminoma. Because of the slow growth rate of seminoma, surveillance must be performed for up to 10 years and typically consists of a history and physical exam and tumor markers (optional) every 3–6 months for year 1, every 6–12 months for years 2–3, and then annually up to 10 years. Imaging while on surveillance includes abdominal and pelvic CT at each visit and CXR as clinically indicated. Seminoma is exquisitely radiosensitive. About 95% of all stage I seminomas are cured with radical orchiectomy and retroperitoneal irradiation (usually 2500–3000 cGy). This low dose of radiation is usually well tolerated, with minimal gastrointestinal side effects. Alternatively, single-agent carboplatin has been used in low-stage seminoma (NCCN, 2015).

Low-volume retroperitoneal disease can also be treated effectively with retroperitoneal irradiation with an average 5-year survival rate of 87%. Prophylactic mediastinal radiation is no longer employed because this may cause considerable myelosuppression and thus compromise the patient's ability to receive chemotherapy if required. Chemotherapy should be used as salvage therapy for patients who relapse following irradiation.

B. High-Stage Seminoma

Patients with bulky seminoma and any seminoma associated with an elevated AFP should receive primary chemotherapy. Seminomas are also sensitive to platinum-based regimens, as are their NSGCT counterparts. Good-risk patients (see discussion later) receive four cycles of etoposide and cisplatin (EP) or three cycles of cisplatin, etoposide, and bleomycin (PEB). Intermediate-risk patients receive four cycles of PEB.

Ninety percent of patients with advanced disease achieve a complete response with chemotherapy. Residual retroperitoneal masses following chemotherapy are often fibrosis (90%) unless the mass is well circumscribed and in excess of 3 cm, under which circumstances approximately 40% of patients harbor residual seminoma. A positron emission tomography (PET) scan should be performed in patients with a residual mass and if positive, surgical resection is warranted. In such cases, surgical excision is warranted.

C. Low-Stage Nonseminomatous Germ Cell Tumors

Standard treatment for stage I disease in the United States has included retroperitoneal lymph node dissection (RPLND). However, because three-fourths of patients with clinical stage I disease are cured by orchiectomy alone and the morbidity of RPLND is not negligible, other alternatives have been explored. These options include surveillance and nerve-sparing RPLND.

Surveillance in stage I NSGCT was proposed because, as mentioned previously, 75% of patients with clinical stage I disease have, in fact, pathologic stage I disease. In addition, infertility related to disruption of sympathetic nerve fibers is common following RPLND. Clinical staging has markedly improved in the presence of CT and MRI scanning. Finally, effective chemotherapy regimens have been developed for relapse. Patients are considered candidates for surveillance if the tumor is an NSGCT confined within the tunica albuginea, the tumor does not demonstrate vascular invasion, tumor markers normalize after orchiectomy, radiographic imaging shows no evidence of disease (CXR, CT), and the patient is considered reliable.

Surveillance should be considered an active process on the part of both the physician and the patient. Patients are followed every 2 months for the first year, 3 months in year 2, 4–6 months in year 3, 6 months in year 4, and annually in year 5 and after. Tumor markers and CXR are obtained at each visit, and CT scans are obtained every 4–6 months in year 1, every 6–12 months in years 2 and 3, every 12 months in year 4 and after. Most relapses occur, however, within the first 8–10 months. With rare exceptions, patients who relapse can be cured by chemotherapy or surgery, or both.

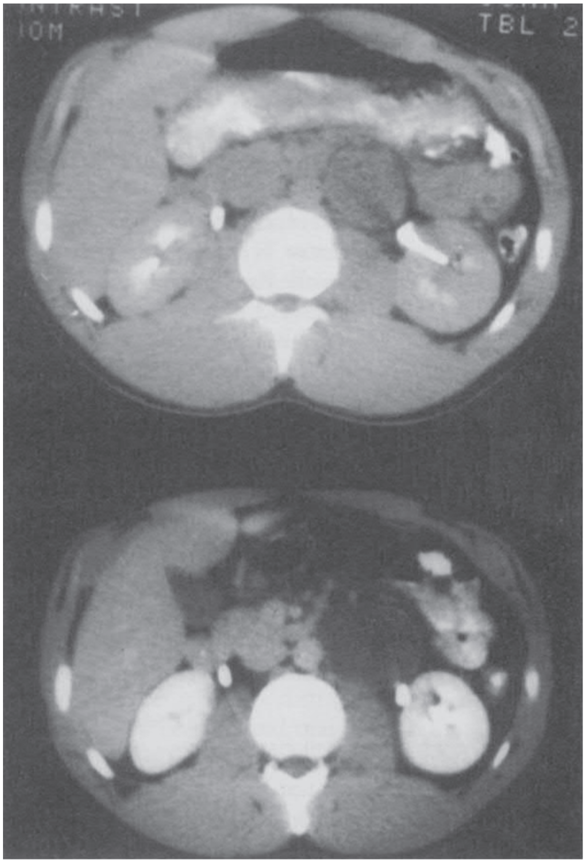
Retroperitoneal lymph node dissection has been the preferred treatment of low-stage NSGCTs in the United States until recently. A thoracoabdominal or midline transabdominal approach may be used, and all nodal tissue between the ureters from the renal vessels to the bifurcation of the common iliac vessels is removed. Patients with negative nodes or N1 disease do not require adjuvant therapy, whereas the recommendation for those with N2 disease is to receive two cycles of chemotherapy because their relapse rate approaches 50%.

While effective in surgically staging and potentially curing a subset of patients, RPLND is associated with significant morbidity, especially with respect to fertility in young men. With a standard RPLND, sympathetic nerve fibers are disrupted, resulting in loss of seminal emission. Currently, a modified RPLND can be performed that preserves ejaculation in up to 90% of patients. By modifying the dissection below the level of the inferior mesenteric artery to include only the nodal tissue ipsilateral to the tumor, important sympathetic fibers from the contralateral side are preserved, thus maintaining emission. Additionally, other surgical techniques such as an open midline extraperitoneal approach (Syan-Bhanvadia et al, 2017) or minimally invasive approaches (laparoscopic/robotic) can minimize morbidity associated with blood loss, ileus, and prolonged length of stay but require longer-term outcomes to determine equivalence in oncologic efficacy.

An alternative approach to patients with clinical stage I disease and vascular invasion in the primary is two cycles of chemotherapy. While obviating the need for surgery, such an approach is associated with neurotoxicity and fertility issues for these young patients.

D. High-Stage Nonseminomatous Germ Cell Tumors

Patients with bulky retroperitoneal disease (>3-cm nodes or three or more 1-cm cuts on CT scan) or metastatic NSGCT are treated with primary platinum-based combination chemotherapy following orchiectomy. Good-risk patients are treated with either four cycles of EP or three cycles of PEB. Intermediate- and poor-risk patients receive four cycles of PEB. If tumor markers normalize and a residual mass is apparent on imaging studies, resection of that mass is mandatory, because 20% of the time it will harbor residual cancer, 40% of the time it will be teratoma, and 40% of the time it will be fibrosis (Figure 22–2). In patients with residual cancer in the resected tissue, the histologic picture is usually embryonal cell carcinoma, but malignant teratoma is seen in <5% of cases. Malignant teratoma is unresponsive to chemotherapy, and only 15% of patients survive following surgical resection. If tumor markers fail to normalize following primary chemotherapy, salvage chemotherapy is required (cisplatin, etoposide, bleomycin, and ifosfamide). Even if patients attain a complete response after chemotherapy (normal tumor markers, no mass on CT scan or CXR), some investigators advocate an RPLND because viable germ cell tumor may be seen in up to 10% of cases.



▲ **Figure 22–2.** ***Upper:*** Computed tomography scan of patient with bulky retroperitoneal mass after radical orchiectomy for embryonal carcinoma. ***Lower:*** Residual cystic mass after chemotherapy; it was resected and found to be teratoma.

Although the treatment plan described cures up to 70% of patients with high-volume disease, there are patients who fail to respond. Also, the potential complications from chemotherapy including sepsis, neuropathy, renal toxicity, and death must be considered. It is thus apparent that it is important to be able to discriminate between patients who are likely to respond to standard chemotherapy (good risk) and those who may require more aggressive regimens (intermediate or high risk). Table 22–3 stratifies patients with advanced testicular cancer into risk groups based on the primary tumor site, location of metastases, and serum tumor markers. The rate of decline of serum tumor markers during chemotherapy has also been used to predict response in patients with advanced disease.

▶ Follow-up Care

All patients with testicular cancer require regular follow-up care. As discussed previously, patients on a surveillance protocol require vigorous follow-up. For those who have undergone surgery (RPLND) or radiotherapy, in general, they are followed at 3-month intervals for the first 2 years, then every

Table 22–3. Risk classification for testicular cancer.

Risk status	Nonseminoma	Seminoma
Good risk	Testicular or retroperitoneal primary No nonpulmonary visceral metastases Postorchiectomy markers S1 level	Any primary site No nonpulmonary visceral metastases Normal AFP, any hCG, any LDH
Intermediate risk	Testicular or retroperitoneal primary No nonpulmonary visceral metastases Postorchiectomy markers S2 level	Any primary site No nonpulmonary visceral metastases Normal AFP, any hCG, any LDH
Poor risk	Mediastinal primary tumor Nonpulmonary visceral metastases Postorchiectomy markers S3 level	None

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactic acid dehydrogenase.

6 months until 5 years, and then yearly. Follow-up visits should include careful examination of the remaining testis, the abdomen, and the lymph node areas. Laboratory investigation should include AFP, hCG, and LDH levels. A CXR and an abdominal film (if an LAG was performed) should also be included at each visit. Abdominal CT scans are used less frequently as risk of relapse in the retroperitoneum is low following RPLND.

Prognosis

Survival in testicular cancer has improved dramatically over the past several years, reflecting the continuing improvement and refinement in combination chemotherapy. For seminoma treated by orchiectomy and radiotherapy, the 5-year disease-free survival rate is 98% for stage I and 92–94% for stage IIA in several recent series. Higher-stage disease treated by orchiectomy and primary chemotherapy has a 5-year disease-free survival rate of 35–75%, yet the lower value comes from older series in which more crude chemotherapy regimens were employed.

Survival in patients with NSGCTs treated by orchiectomy and RPLND for stage I disease ranges from 96% to 100%. For low-volume stage II disease treated with chemotherapy plus surgery, >90% 5-year disease-free survival rates are attainable. Patients with bulky retroperitoneal or disseminated disease treated with primary chemotherapy followed by surgery have a 5-year disease-free survival rate of 55–80%.

NON-GERM CELL TUMORS OF THE TESTIS

Approximately 5–6% of all testis tumors are non-germ cell tumors of the testis. Three types will be considered: Leydig cell tumors, Sertoli cell tumors, and gonadoblastomas.

Leydig Cell Tumors

A. Epidemiology and Pathology

Leydig cell tumors are the most common non–germ cell tumors of the testis and account for 1–3% of all testicular tumors. They follow a bimodal age distribution: the 5- to 9-year-old and the 25–35-year-old age groups. Twenty-five percent of these tumors occur in childhood. Bilaterality is seen in 5–10% of cases. The cause of these tumors is unknown; unlike germ cell tumors, there is no association with cryptorchidism.

Pathologic examination reveals a small, yellow, well-circumscribed lesion devoid of hemorrhage or necrosis. Microscopically, hexagonally shaped cells with granular, eosinophilic cytoplasm containing lipid vacuoles are seen. Reinke crystals are fusiform-shaped cytoplasmic inclusions that are pathognomonic for Leydig cells.

B. Clinical Findings

Prepubertal children usually present with virilization, and tumors are benign. Adults are usually asymptomatic, although gynecomastia may be present in 20–25%. Ten percent of tumors in adults are malignant. Laboratory findings include elevated serum and urinary 17-ketosteroids as well as estrogens.

C. Treatment and Prognosis

Radical orchiectomy is the initial treatment for Leydig cell tumors. Clinical staging is similar to that for germ cell tumors, and levels of the 17-ketosteroids can be helpful in distinguishing between benign and malignant lesions. Elevations of 10–30 times normal are typical of malignancy. RPLND is recommended for malignant lesions. Because of the rarity of these lesions, the role of chemotherapy remains to be defined. Prognosis is excellent for benign lesions, while it remains poor for patients with disseminated disease.

Sertoli Cell Tumors

A. Epidemiology and Pathology

Sertoli cell tumors are exceedingly rare, composing <1% of all testicular tumors. A bimodal age distribution is seen: 1-year old or younger and the 20- to 45-year-old age group. Approximately 10% of the lesions are malignant. Gross examination reveals a yellow or gray-white lesion with cystic components. Benign lesions are well circumscribed, while malignant lesions show ill-defined borders. Microscopically, tumors appear heterogeneous with mixed amounts of epithelial and stromal components. Sertoli cells are columnar or hexagonal cells with a large nucleus and solitary nucleolus and contain vacuolated cytoplasm.

B. Clinical Findings

A testicular mass is the most common presentation. Virilization is often seen in children, and gynecomastia may be present in 30% of adults. Because of the rarity of these tumors, minimal endocrine data on these patients are available.

C. Treatment

Radical orchiectomy is the initial procedure of choice. In cases of malignancy, RPLND is indicated; however, the roles of chemotherapy and radiotherapy remain unclear.

Gonadoblastomas

A. Epidemiology and Pathology

Gonadoblastomas represent 0.5% of all testicular tumors and are seen almost exclusively in patients with some form of gonadal dysgenesis. Most of these tumors occur in patients younger than 30 years, although the age distribution ranges from infancy to >70 years. Gross examination reveals a yellow or gray-white lesion that can vary in size from microscopic to >20 cm and may exhibit calcifications. Microscopically, three cell types are seen: Sertoli cells, interstitial cells, and germ cells.

B. Clinical Findings

The clinical manifestations are predominantly related to the underlying gonadal dysgenesis and are discussed elsewhere in this book. It is noteworthy that four-fifths of patients with gonadoblastomas are phenotypic females. Males typically have cryptorchidism or hypospadias.

C. Treatment and Prognosis

Radical orchiectomy is the primary treatment of choice. In the presence of gonadal dysgenesis, a contralateral gonadectomy is recommended because the tumor tends to be bilateral in 50% of cases in this setting. Prognosis is excellent.

SECONDARY TUMORS OF THE TESTIS

Secondary tumors of the testis are rare. Three categories are considered: lymphoma, leukemia, and metastatic tumors.

Lymphoma

A. Epidemiology and Pathology

Lymphoma is the most common testicular tumor in a patient older than 50 years and is the most common secondary neoplasm of the testis, accounting for 5% of all testicular tumors. It may be seen in three clinical settings: (1) late manifestation of widespread lymphoma, (2) initial presentation of clinically occult disease, and (3) primary extranodal disease. Gross examination reveals a bulging, gray or pink lesion with ill-defined margins. Hemorrhage and necrosis are common. Microscopically, diffuse histiocytic lymphoma is the most common type.

B. Clinical Findings

Painless enlargement of the testis is common. Generalized constitutional symptoms occur in one-fourth of patients. Bilateral testis involvement occurs in 50% of patients, usually asynchronously.

C. Treatment and Prognosis

Fine-needle aspiration should be considered in patients with a known or suspected diagnosis of lymphoma while radical orchiectomy is reserved for those with suspected primary lymphoma of the testicle. Further staging and treatment should be handled in conjunction with the medical oncologist. Prognosis is related to the stage of disease. Some reports support adjuvant chemotherapy for primary testicular lymphoma, with improved survival rates of up to 93% after 44 months of follow-up.

Leukemic Infiltration of the Testis

The testis is a common site of relapse for children with acute lymphocytic leukemia. Bilateral involvement may be present in one-half of cases. Testis biopsy rather than orchiectomy is the diagnostic procedure of choice. Bilateral testicular irradiation with 20 Gy and reinstitution of adjuvant chemotherapy constitute the treatment of choice. Prognosis remains guarded.

Metastatic Tumors

Metastasis to the testis is rare. These lesions are typically incidental findings at autopsy. The most common primary site is the prostate, followed by the lung, gastrointestinal tract, melanoma, and kidney. The typical pathologic finding is neoplastic cells in the interstitium with relative sparing of the seminiferous tubules.

EXTRAGONADAL GERM CELL TUMORS

Epidemiology and Pathology

Extragonadal germ cell tumors are rare, accounting for approximately 3% of all germ cell tumors. Debate continues over whether these lesions originate from "burned-out" testicular primaries or originate de novo. Most retroperitoneal tumors have their origin from a testicular primary, whereas mediastinal germ cell tumors are truly ectopic.

The most common sites of origin in decreasing order are mediastinum, retroperitoneum, sacrococcygeal area, and pineal gland. All germ cell types may be observed. Seminoma composes more than half of the retroperitoneal and mediastinal tumors.

Clinical Findings

Clinical presentation depends on the site and volume of disease. Mediastinal lesions may present with pulmonary complaints. Retroperitoneal lesions may present with abdominal or back pain and a palpable mass. Sacrococcygeal tumors are most commonly seen in neonates and may present with a palpable mass and bowel or urinary obstruction. Pineal tumors may present with headache, visual or auditory complaints, or hypopituitarism.

Metastatic spread is to regional lymph nodes, lung, liver, bone, and brain. Metastatic workup is similar, therefore, to that of testicular germ cell tumors. A careful testicular examination is mandatory along with ultrasonography to exclude an occult testicular primary.

Treatment and Prognosis

Treatment of extragonadal germ cell tumors parallels that of testicular tumors. Low-volume seminoma can be managed with radiotherapy. High-volume seminoma should receive primary chemotherapy. Prognosis parallels that of testicular seminoma. Primary chemotherapy should be employed for nonseminomatous elements with surgical excision of residual masses; however, prognosis remains poor for these patients.

TUMORS OF THE EPIDIDYMIS, PARATESTICULAR TISSUES, SPERMATIC CORD

Primary tumors of the epididymis are rare and are most commonly benign. Adenomatoid tumors of the epididymis are the most common and typically occur in the third and fourth decades of life. They are typically asymptomatic, solid lesions that arise from any portion of the epididymis.

Leiomyomas are the second most common tumor of the epididymis. These lesions tend to be painful and are often associated with a hydrocele. Cystadenomas are benign lesions of the epididymis that are bilateral in 30% of cases and are frequently seen in association with von Hippel–Lindau disease. Histologically, these lesions are difficult to distinguish from renal cell carcinoma. Malignant lesions of the epididymis are extremely rare. In general, an inguinal approach should be used, and if frozen section confirms a benign lesion, epididymectomy should be performed. If a malignant tumor is diagnosed, radical orchiectomy must be performed.

Tumors of the spermatic cord are typically benign. Lipomas of the cord account for most of these lesions. Of the malignant lesions, rhabdomyosarcoma is the most common, followed by leiomyosarcoma, fibrosarcoma, and liposarcoma.

Clinical diagnosis of tumors of the spermatic cord can be difficult. Differentiating between a hernia and a spermatic cord tumor may be possible only at exploration. In general, these lesions should be approached through an inguinal incision. The cord should be occluded at the internal ring and frozen sections obtained. If malignancy is diagnosed, attention should be directed toward performing wide local excision to avoid local recurrence. Staging of disease is similar to that of testicular tumors. For rhabdomyosarcoma, RPLND should be performed with adjuvant radiotherapy and chemotherapy. The value of RPLND for the other malignant spermatic cord tumors remains to be determined. Prognosis relates to the histologic status, stage, and site of disease.

TUMORS OF THE PENIS

Epidemiology and Risk Factors

Carcinoma of the penis accounts for <1% of cancers among males in the United States, with approximately one to two new cases reported per 100,000 men. There is marked variation in incidence with geographic location. In areas such as Africa and regions of South America, penile carcinoma may compose 10–20% of all malignant lesions. Penile carcinoma occurs most commonly after the fifth decade in life, although rare case reports have included children.

Several clinical and sociodemographic factors have been associated with the development of penile cancer or associated lesion such as smoking, chronic inflammatory conditions, poor genital hygiene, lack of circumcision, phimosis, and low socioeconomic status. The disease is virtually unheard of in males circumcised near birth. One theory postulates that smegma accumulation under the phimotic foreskin results in chronic inflammation leading to carcinoma. Human papillomavirus (HPV) is implicated in approximately 50% of penile cancers and has gained more attention recently following the development of a vaccine and causative roles in cervical and oropharyngeal cancers.

Pathology

A. Precancerous Dermatologic Lesions

Leukoplakia is a rare condition that most commonly occurs in diabetic patients. A white plaque typically involving the meatus is seen. Histologic examination reveals acanthosis, hyperkeratosis, and parakeratosis. This lesion may precede or occur simultaneously with penile carcinoma.

Balanitis xerotica obliterans is a white patch originating on the prepuce or glans and usually involving the meatus. The condition is most commonly observed in middle-aged diabetic patients. Microscopic examination reveals atrophic epidermis and abnormalities in collagen deposition.

Giant condylomata acuminata are cauliflower-like lesions arising from the prepuce or glans. The cause is believed to be viral (HPV). These lesions may be difficult to distinguish from well-differentiated squamous cell carcinoma.

B. Penile Intraepithelial Neoplasia (Carcinoma In Situ, Bowen's Disease, Erythroplasia of Queyrat)

Penile intraepithelial neoplasia (PeIN) is a squamous cell carcinoma in situ typically involving the penile glans (erythroplasia of Queyrat) or shaft (Bowen's disease). The lesion appears as a red plaque or velvety lesion with ulcerations or encrustations. Microscopic examination shows typical, hyperplastic cells in a disordered array with vacuolated cytoplasm and mitotic figures. This can be further subdivided into differentiated or undifferentiated subtypes (associated with HPV positivity).

C. Invasive Carcinoma of the Penis

Squamous cell carcinoma represents most penile cancers. It most commonly originates on the glans, with the next most common sites, in order, namely, the prepuce and the shaft. The appearance may be papillary or ulcerative.

Verrucous carcinoma is a variant of squamous cell carcinoma representing 5–16% of penile carcinomas. This lesion is papillary in appearance, and on histologic examination, it is noted to have a well-demarcated deep margin unlike the infiltrating margin of the typical squamous cell carcinoma.

Patterns of Spread

Invasive carcinoma of the penis begins as an ulcerative or papillary lesion, which may gradually grow to involve the entire glans or shaft of the penis. Buck's fascia represents a barrier to corporal invasion and hematogenous spread. Primary dissemination is via lymphatic channels to the femoral and iliac nodes. The prepuce and shaft skin drain into the superficial inguinal nodes (superficial to fascia lata), while the glans and corporal bodies drain to both superficial and deep inguinal nodes (deep to fascia lata). There are many cross-communications so that penile lymphatic drainage is bilateral to both inguinal areas. Drainage from the inguinal nodes is to the pelvic nodes. Involvement of the femoral nodes may result in skin necrosis and infection or femoral vessel erosion and hemorrhage. Distant metastases are clinically apparent in <10% of cases and may involve lung, liver, bone, or brain.

Tumor Staging

The staging system used most commonly in the United States was proposed by Jackson (1966), and the stages are as follows. In stage I, the tumor is confined to the glans or prepuce. Stage II involves the penile shaft. Stage III has operable inguinal node metastasis. In stage IV, the tumor extends beyond the penile shaft, with inoperable inguinal or distant metastases. The TNM classification of the American Joint Committee (2010) is given in Table 22–4.

Clinical Findings

A. Symptoms

The most common complaint at presentation is the lesion itself. It may appear as an area of induration or erythema, an ulceration, a small nodule, or an exophytic growth. Phimosis may obscure the lesion and result in a delay in seeking medical attention. In fact, 15–50% of patients delay for at least 1 year in seeking medical attention. Other symptoms include pain, discharge, irritative voiding symptoms, and bleeding.

B. Signs

Lesions are typically confined to the penis at presentation. The primary lesion should be characterized with respect to size, location, and potential corporal body involvement. Careful palpation of the inguinal area is mandatory because >50% of patients present with enlarged inguinal nodes. This enlargement may be secondary to inflammation or metastatic spread.

C. Laboratory Findings

Laboratory evaluation is typically normal. Anemia and leukocytosis may be present in patients with longstanding disease or extensive local infection. Hypercalcemia in the absence of osseous metastases may be seen in 20% of patients and appears to correlate with volume of disease.

D. Imaging

Metastatic workup should include CXR, bone scan, and CT scan of the abdomen and pelvis. Disseminated disease is present in <10% of patients at presentation.

Differential Diagnosis

In addition to the dermatologic lesions discussed previously, carcinoma of the penis must be differentiated from several infectious lesions. Syphilitic chancre may present as a painless ulceration. Serologic and darkfield examination should establish the diagnosis. Chancroid typically appears as a painful ulceration of the penis. Selective cultures for *Haemophilus ducreyi* should identify the cause. Condylomata acuminata appear as exophytic, soft, "grape cluster" lesions anywhere on the penile shaft or glans. Biopsy can distinguish this lesion from carcinoma if any doubt exists.

Treatment

A. Primary Lesion

Biopsy of the primary lesion is mandatory to establish the diagnosis of malignancy. Treatment varies depending on the pathology as well as the location of the lesion. CIS may be treated conservatively in reliable patients. Fluorouracil cream application or neodymium:YAG laser treatment is effective for CIS and in preserving of the penis. Patients must come for frequent follow-up examinations to monitor response.

The goal of treatment in invasive penile carcinoma is complete excision with adequate margins. For lesions involving the prepuce, this may be accomplished by simple circumcision. For lesions involving the glans or distal shaft, partial penectomy with a 2-cm margin to decrease local recurrence has traditionally been suggested. Less aggressive surgical resections such as Mohs micrographic surgery and local excisions directed at penile preservation yet attaining a negative surgical margin have gained popularity. For lesions involving the proximal shaft, or when partial penectomy results in a penile stump of insufficient length for sexual function or directing the urinary stream, total penectomy with perineal urethrostomy has been recommended.

B. Regional Lymph Nodes

As discussed previously, penile carcinoma spreads primarily to the inguinal lymph nodes. However, enlargement of

Table 22–4. AJCC TNM staging (2010).

DEFINITIONS OF AJCC TNM
Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (Penile) intraepithelial neoplasia (PeINJ)
Ta	Noninvasive localized squamous cell carcinoma
T1	Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade
T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)
T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
T3	Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion
T4	Tumor invades into adjacent structures (i.e., scrotum prosate, pubic bone)

Pathological N (pN)

pN Category	pN Criteria
pNX	Lymph node metastasis cannot be established
pN0	No lymph node metastasis
pN1	≤ 2 unilateral inguinal metastases, no ENE
pN2	≥ 3 unilateral inguinal metastases or bilateral metastases, no ENE
pN3	ENE of lymph node metastases or pelvic lymph node metastases

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis present

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
Tia	N0	M0	0 is
Ta	N0	M0	0a
T1a	N0	M0	I
T1b	N0	M0	
T2	N	M0	IIA
T3	N0	M0	IIB
T1-3	N1	M0	IIIA
T1-3	N2	M0	IIIB
T4	Any N	M0	IV
Any T	N3	M0	IV
Any T	Any N	M1	IV

HISTOLOGIC GRADE (G)

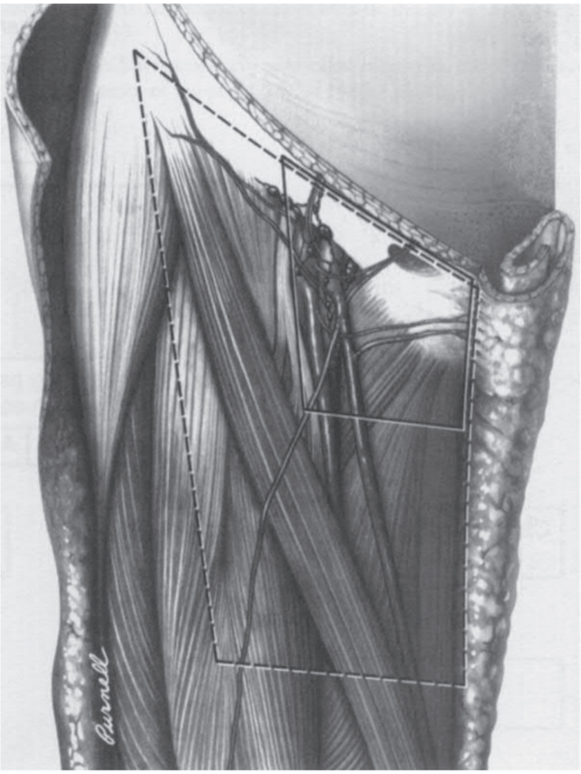
G	G Defination
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated/high grade

[a] Broad pushing penetration (invasion) is permitted; destructive invasion is not consistent with Ta stage.

LVI,- lymphovascular invasion.

Used with the permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al. (Eds.) *AJCC Cancer Staging Manual,* 8th Ed. Springer New York, 2017.

inguinal nodes at presentation does not necessarily imply metastatic disease. In fact, up to 50% of the time this enlargement is caused by inflammation. Thus, patients who present with enlarged inguinal nodes that are neither bulky (<4 cm) nor fixed can proceed with a diagnostic fine-needle aspiration (FNA) or proceed directly to inguinal lymph node dissection. If the FNA is nondiagnostic, an excisional or sentinel node biopsy described by Cabanas (1977) or a modified (limited) dissection as suggested by Catalona (1988) (Figure 22–3) can be done. A 4–6-week course of oral broad-spectrum antibiotics can be considered but is no longer used routinely. In the absence of nodal disease observation in low-stage primary tumors (Tis, T1) is warranted and a dynamic sentinel lymph node biopsy can be considered. In patients with high-stage tumors (cT2 or greater) and poor prognostic risk factors (eg, >50% poorly differentiated disease and lymphovascular invasion), it is reasonable to consider bilateral sentinel lymph node biopsy or more commonly bilateral superficial lymph node dissection and possibly deep dissection if any positive nodes are encountered. Patients who initially have clinically negative nodes but in whom clinically palpable nodes later develop should undergo a unilateral ilioinguinal node dissection.



▲ **Figure 22–3.** Comparison of limits of dissection of complete (dashed line) versus limited (solid line) inguinal lymphadenectomy.

Patients who have palpable bulky nodes (≥4 cm), fixed nodes, or inoperable disease are treated with chemotherapy (cisplatin and 5-fluorouracil) after diagnosis with biopsy or FNA is made. If there is tumor regression after neoadjuvant chemotherapy with or without radiotherapy, consolidative surgery with superficial and deep inguinal node dissection can be considered. In some cases, regional radiotherapy can provide significant palliation by delaying ulceration and infectious complications and alleviating pain.

C. Systemic Disease

Four chemotherapeutic agents demonstrate activity against penile carcinoma: bleomycin, methotrexate, cisplatin, and 5-fluorouracil. However, no long-term responders have been reported.

▶ Prognosis

Survival in penile carcinoma correlates with the presence or absence of nodal disease. Five-year survival rates for patients with node-negative disease range from 65% to 90%. For patients with positive inguinal nodes, this rate decreases to 30–50% and with positive iliac nodes decreases to <20%. In the presence of soft tissue or bony metastases, no 5-year survivors have been reported.

▶ Other Penile Tumors

Squamous cell carcinoma accounts for 98% of penile cancers. Sporadic cases of melanoma, basal cell carcinoma, and Paget disease have been reported. The incidence of Kaposi sarcoma of the penis is increasing with the increasing prevalence of the human immunodeficiency virus. It appears as a painful papule on the glans or shaft with bluish-purple discoloration. These lesions tend to be radiosensitive.

TUMORS OF THE SCROTUM

Tumors of the scrotal skin are rare. The most common benign lesion is a sebaceous cyst. Squamous cell carcinoma is the most common malignant tumor of the scrotum, although rare cases of melanoma, basal cell carcinoma, and Kaposi sarcoma have been reported. In the past, squamous cell carcinoma of the scrotum most commonly resulted from exposure to environmental carcinogens, including chimney soot, tars, paraffin, and some petroleum products. Today, most cases result from poor hygiene and chronic inflammation.

Biopsy of the scrotal lesion must be performed to establish a histologic diagnosis. Wide excision with a 2-cm margin should be performed for malignant tumors. The surrounding subcutaneous tissue should be excised with the primary tumor; however, resection of the scrotal contents is rarely necessary. Primary closure using the redundant scrotal skin is usually possible. The management of inguinal nodes should be similar to that of penile cancer.

Prognosis correlates with the presence or absence of nodal involvement. In the presence of inguinal node metastasis, the 5-year survival rate is approximately 25%; there are virtually no survivors if iliac nodes are involved.

BIBLIOGRAPHY

Tumors of the Testis

AJCC (American Joint Committee on Cancer): Cancer Staging Manual. 7th ed. Springer-Verlag, New York, 2017.

Berthelsen JG et al: Screening for carcinoma in situ of the contralateral testis in patients with germinal testicular cancer. Br Med J 1982;285:1683.

Boden G, Gibb R: Radiotherapy and testicular neoplasms. Lancet 1951;2:1195.

Hyams ES et al: Laparoscopic retroperitoneal lymph node dissection for clinical stage 1 nonseminomatous germ cell tumor: A large single institution experience. J Urol 2012;187:487–492.

NCCN (National Comprehensive Cancer Network): Clinical Practice Guidelines in Oncology: Testicular Cancer, 2015. (Available online at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.)

Pettersson A et al: Age at surgery for undescended testis and risk of testicular cancer. New Engl J Med 2007;356:1835.

Syan-Bhanvadia S et al: Midline extraperitoneal approach to retroperitoneal lymph node dissection in testicular cancer: minimizing surgical morbidity. Eur Urol 2017;72(5):814–820.

Tumors of the Penis

Cabanas RM: An approach for the treatment of penile carcinoma. Cancer 1977;39:456.

Carroll PR, Presti JC Jr: Testis cancer. Urol Clin North Am 1998; 25(3): entire issue.

Catalona WJ: Modified inguinal lymphadenectomy for carcinoma of the penis with preservation of saphenous veins: Technique and preliminary results. J Urol 1988;140:306.

Jackson SM: The treatment of carcinoma of the penis. Br J Surg 1966;53:33.

Urinary Diversion and Bladder Substitutions

23

Maxwell V. Meng, MD, MPH; Susan Barbour, RN, MS, WOCN; &
Peter R. Carroll, MD, MPH

Selected patients with lower urinary tract cancers or severe functional or anatomic abnormalities of the bladder may require urinary diversion. Although this can be accomplished by establishing direct contact between the urinary tract and the skin surface, it is most often performed by incorporating various intestinal segments into the urinary tract. Virtually every segment of the gastrointestinal tract has been used to create urinary reservoirs or conduits. No single technique is ideal for all patients and clinical situations. The decision is based on a patient's underlying disease and optimal method of treatment as well as on renal function, individual anatomy, and personal preference. An ideal method of urinary diversion would most closely approximate the normal bladder; it would be nonrefluxing, low-pressure, continent, and nonabsorptive.

Individual methods of urinary diversion can be categorized in various ways, such as by (1) the segment of intestine used and (2) whether the method provides complete continence or simply acts as a conduit carrying urine from the renal pelvis or ureter to the skin, where the urine is collected in an appliance attached to the skin surface. Continent forms of urinary diversion can be categorized further according to whether they are attached to the urethra (ie, as a bladder substitute) or are placed in the abdomen and rely on another mechanism for continence (continent urinary reservoir).

PREOPERATIVE COUNSELING AND PREPARATION

All candidates for urinary diversion and bladder substitution should undergo careful preoperative counseling and preparation, including a detailed discussion of the goals and potential complications of each method. Any potential impact of a procedure on sexual function, body image, and lifestyle should be discussed. Overall satisfaction of most patients undergoing urinary diversion appears to be high (Allareddy et al, 2006; Dutta et al, 2002; Fujisawa et al, 2000; Hara et al, 2002). However, because they allow freedom from an external appliance, continent forms of urinary diversion, especially bladder substitution, may be of great psychological and functional benefit to well-selected patients (Bjerre et al, 1995; Okada et al, 1997). More recent data suggest that the differences in quality of life between continent and noncontinent diversion may not be as significant as previously predicted (Gilbert et al, 2007).

A careful history taken from the patient should note any previous abdominal or pelvic surgery, irradiation, or systemic disease. A history of intestinal resection or irradiation, renal insufficiency, diverticulitis, regional enteritis, or ulcerative colitis would be especially important to consider when selecting a method of urinary diversion or bladder substitution. A complete blood count and measurement of serum electrolytes, urea nitrogen, and creatinine should be performed. The upper urinary tract should be imaged with ultrasound or computed tomography to determine whether hydronephrosis, renal parenchymal scarring, or calculous disease exists. Contrast imaging of the small or large bowel or colonoscopy should be considered preoperatively for patients with a history of significant intestinal irradiation, occult bleeding, or other gastrointestinal diseases. Patients with benign bladder diseases—such as a reduced bladder capacity due to neurologic disorders or irradiation, bladder fistulas, or interstitial cystitis—are occasionally considered candidates for urinary diversion or bladder substitution to manage urinary incontinence; however, with such patients, careful evaluation of bladder function and anatomy is required, as adequate urinary function can often be restored by urinary tract reconstruction, pharmacologic manipulation, or intermittent catheterization.

Patients undergo a standard mechanical and oral antibiotic bowel cleansing program beginning 1 or 2 days before surgery. Recent data suggest that mechanical bowel preparation can be avoided in colon and rectal surgery without increased risk of postoperative infectious complications and may in fact contribute to postoperative ileus. Hence use of clear liquid diet without mechanical bowel preparation prior to surgery may be adequate in most cases (Slim et al, 2009). Administration of combined oral and intravenous antibiotics prior to bowel surgery is advised as it appears to reduce the risk of wound infections by as much as 75% (Nelson et al, 2009). Much of patients' dissatisfaction with urinary diversion can be attributed to poor stomal construction or siting (Fitzgerald et al, 1997). The patient should be preoperatively evaluated in the lying, sitting, and standing positions with clothes on. The stoma should be located above or below the belt line. The most common site for stoma placement is through the rectus abdominis muscle sheath to reduce the later development of a parastomal hernia. The ideal location is free of creases, folds, previous incisions, and in a location visible to the patient to ensure ability to care for stoma. In obese patients or patients with a short mesentery, the stoma should be placed closer to the level of the umbilicus or in the right upper quadrant.

INTESTINAL CONDUIT URINARY DIVERSION

Ileal Conduit

Ureteroileal urinary diversion is the most common method of urinary diversion in the United States. The conduit is constructed using a segment of ileum 18–20 cm long and located approximately 15–20 cm proximal to the ileocecal valve (Figure 23–1). Longer conduits may be required in obese patients, but a short segment minimizes the absorptive surface of the bowel in contact with urine. Once the appropriate length of bowel is selected and isolated, the mesentery is divided proximally and distally, and individual mesenteric blood vessels are ligated. The bowel is divided, thus isolating the segment selected for conduit construction. The continuity of the small intestine is reestablished, and the anastomosis is positioned above the plane of the conduit to allow for normal bowel function. The conduit is usually positioned in the right lower quadrant of the abdomen in an isoperistaltic direction. The posterior closed end of the conduit can be fixed to the posterior peritoneum or the sacral promontory to prevent volvulus of the conduit. The ureters are reimplanted individually in an end-to-side fashion (Bricker technique) or joined together (Wallace technique) and anastomosed in an end-to-end fashion, creating a refluxing ureteroileal anastomosis. Ureteral stents (7–8 Fr, single-J, Silastic) are usually placed through the ureteral anastomosis and conduit into the renal pelvis to facilitate urinary drainage while the anastomosis is healing.

The preselected stoma site is identified and a small circle of skin and underlying fat excised. The fascia is incised in a cruciate fashion. The distal end of the conduit is brought through the rectus abdominis muscle and anchored to the fascia, and the stoma is then formed. The stoma should protrude, without tension, approximately 1–1.5 in above the skin surface.

Jejunal Conduit

Jejunal conduit urinary diversion is used rarely and mainly in cases where other segments cannot be used because of the risk for significant ileal and colonic disease caused by previous irradiation or inflammatory bowel disease. Electrolyte disturbances are more common when the jejunum is used for conduit construction, and hence this bowel segment is used only if none of the other intestinal segments can be used to fashion a conduit.

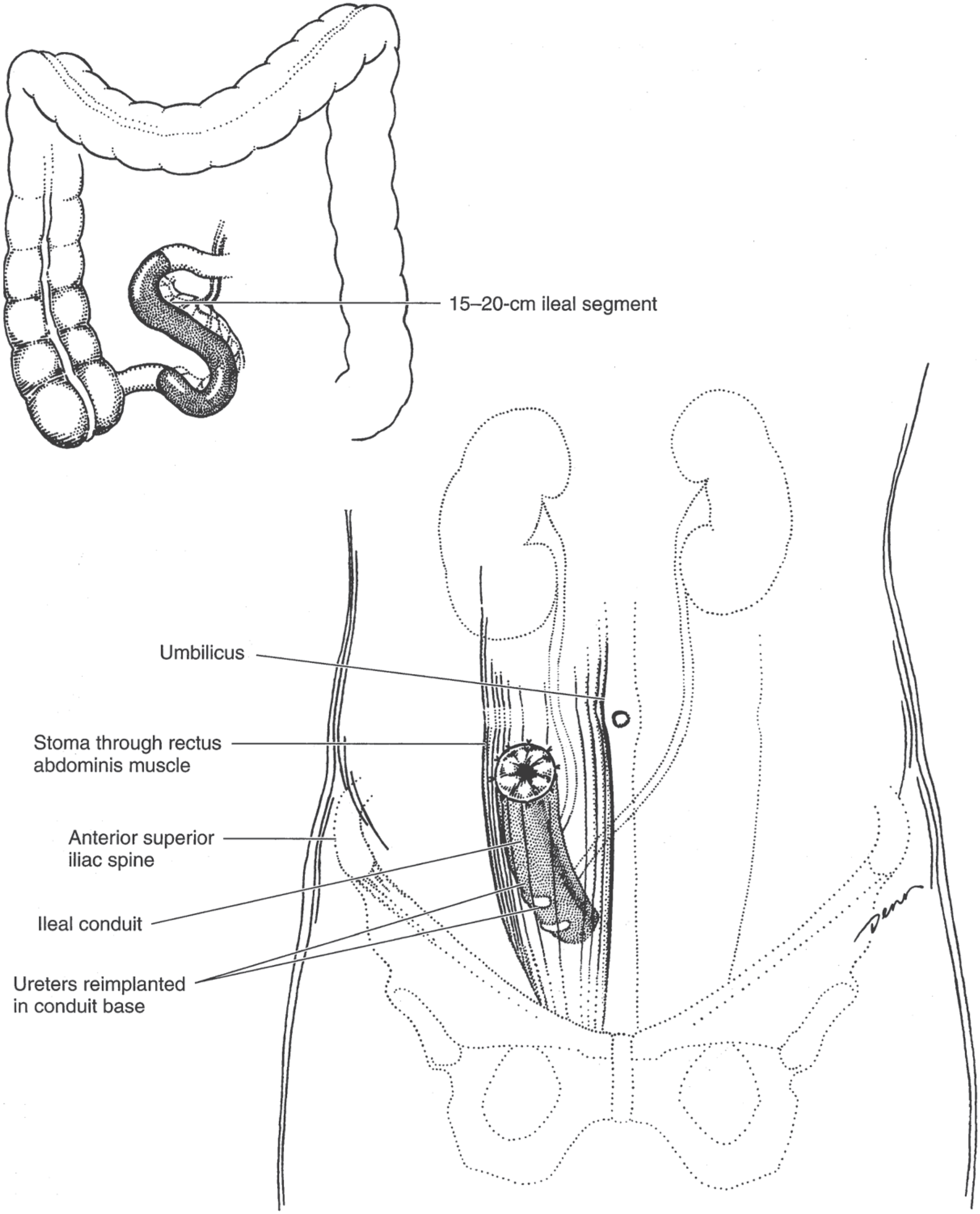
Colon Conduit

There are several advantages to using the large bowel in construction of urinary conduits. Nonrefluxing ureterointestinal anastomoses are easily performed, possibly abrogating the deleterious effects of reflux on the upper urinary tracts (Richie and Skinner, 1975); stomal stenosis is uncommon because of the wide diameter of the large bowel; limited absorption of electrolytes occurs; and the blood supply to the transverse and sigmoid colon is abundant. Either the transverse or the sigmoid colon can be used, allowing for placement of the conduit high or low in the abdomen, depending on the integrity and condition of the ureters. Use of the transverse colon is especially well suited for patients who have received extensive pelvic irradiation or when the middle and distal ureters are absent.

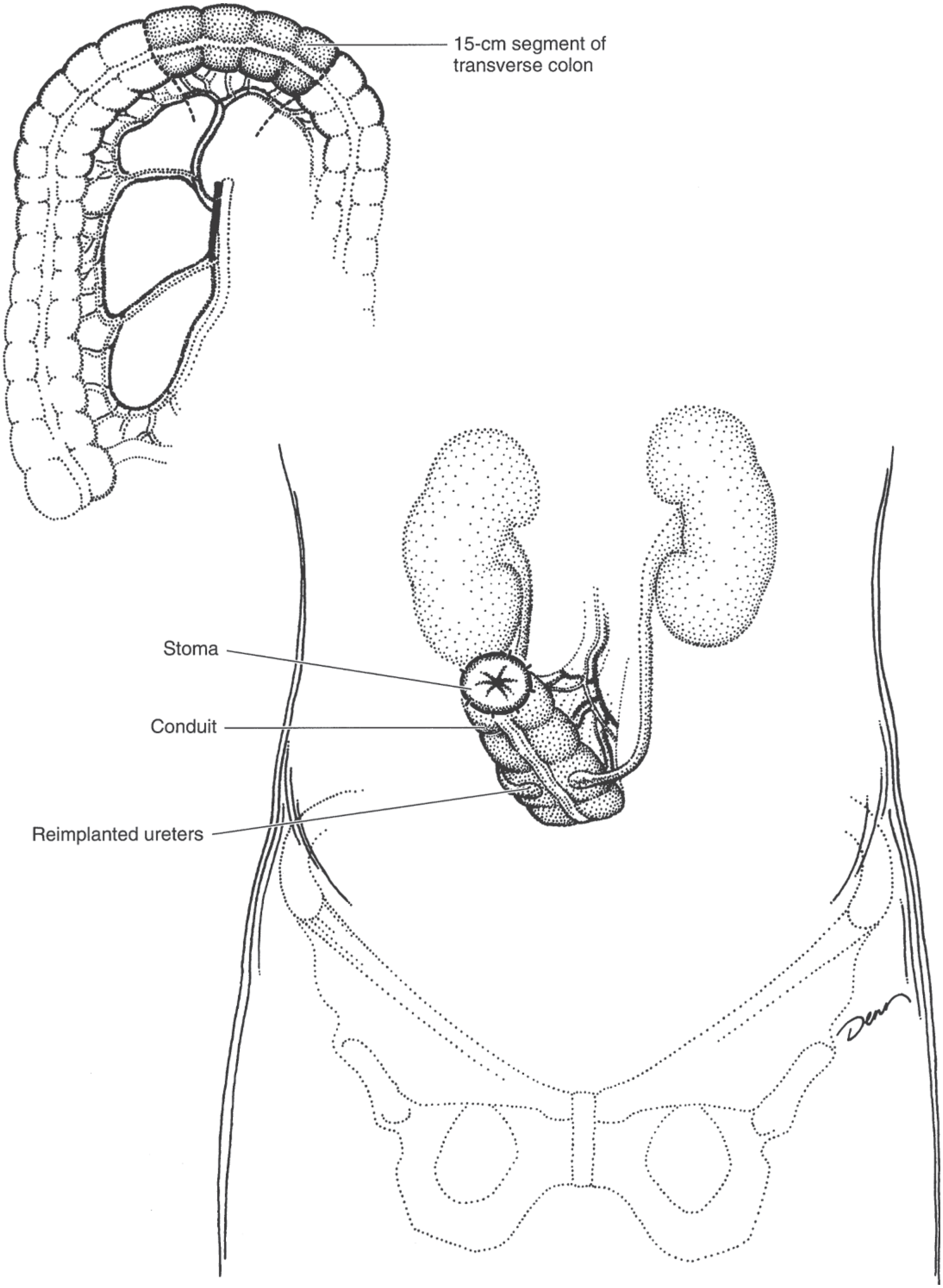
The blood supply of the transverse colon is based on the middle colic artery. The greater omentum is separated from the superior surface of the transverse colon, and a segment of bowel, usually 15 cm in length, is selected for the conduit (Figure 23–2). Short mesenteric incisions are made, and the colon is divided proximally and distally. Once the conduit is isolated, bowel continuity is reestablished. The proximal end of the conduit is closed and fixed in the midline posteriorly. The ureters are brought through small incisions in the posterior peritoneum and reimplanted into the base of the conduit. The stoma may be positioned on either the patient's right or left side.

A sigmoid conduit is constructed in a similar manner. Great care should be taken to preserve the blood supply by carefully selecting a segment with a good blood supply and by making short mesenteric incisions. The conduit is positioned lateral to the reapproximated sigmoid colon. Ureteral reimplantation and stoma construction are completed.

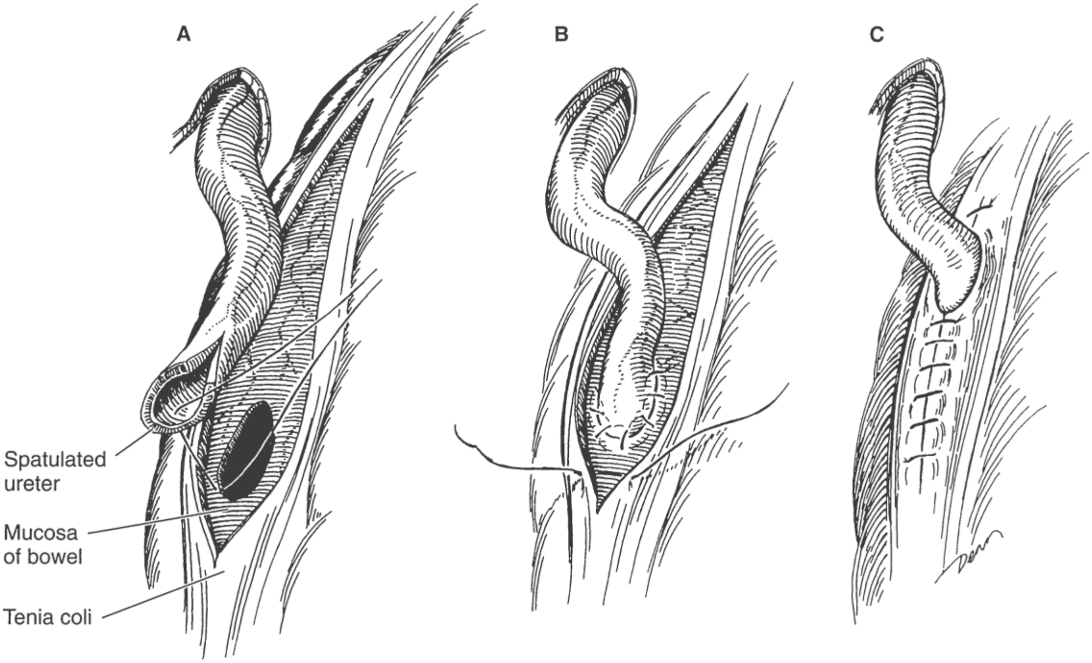
The ureters can be reimplanted into the large intestine either in a nonrefluxing submucosal tunnel or in a refluxing end-to-side manner. A submucosal tunnel can be created by incising the tenia up to the mucosa of the large bowel for a length of 3–4 cm. A "button" of mucosa is removed, and the ureter is anastomosed to the mucosa of the bowel. The muscularis of the tenia is reapproximated over the ureter to complete the tunnel (Figure 23–3).


15–20-cm ileal segment
Umbilicus
Stoma through rectus abdominis muscle
Anterior superior iliac spine
Ileal conduit
Ureters reimplanted in conduit base

▲ **Figure 23–1.** Ileal conduit.



▲ **Figure 23–2.** Transverse colon conduit.



▲ **Figure 23–3.** Creation of a submucosal tunnel in the wall of the colon to prevent ureteral reflux of urine. ***A:*** Incision in the tenia coli. ***B:*** Anastomosis of distal ureter to large intestine mucosa. ***C:*** Muscularis (tenia) approximated over ureter.

CONTINENT URINARY DIVERSION AND BLADDER SUBSTITUTION

General Considerations

Various procedures have been developed for construction of bladder substitutes or continent urinary reservoirs that preclude the need for an external urine collection appliance. Such reservoirs or bladder substitutes are composed of three segments: ureterointestinal (afferent limb) anastomosis, the reservoir itself, and the conduit carrying the urine from the reservoir to the surface (efferent continence mechanism). Bladder substitutes rely on the intact urethra and sphincter to provide outlet resistance and carry urine to the urethral meatus. In men and women whose urethrae are involved by cancer or are not functional owing to benign diseases, an efferent continence mechanism can be constructed with the appendix or short segments of tapered, intussuscepted, or reimplanted intestine.

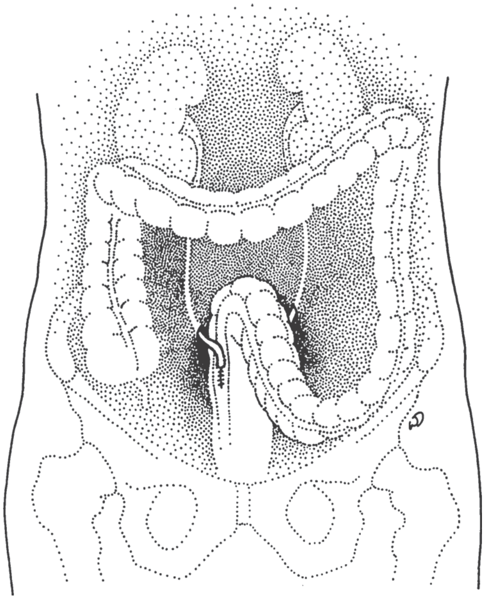
The decision to proceed with bladder replacement is contingent on the risk of urethral recurrence and the continence of the patient. Both men and women who have low risk of urethral recurrence and those who have intact external urinary sphincters should be considered for bladder replacement rather than construction of a continent urinary reservoir. The risk of urethral occurrence or recurrence in men who undergo radical cystectomy is 6.1–10.6%. Carcinoma in situ and tumor multifocality appear to be risk factors for prostatic urethral tumor involvement in men with bladder cancer (Nixon et al, 2002). Although prostatic urethral disease is a risk factor for urethral recurrence, more recent evidence suggests that orthotopic diversion may be considered in those with only proximal prostatic urethral involvement and negative urethral margins at cystectomy (Iselin et al, 1997). Although orthotopic bladder replacement was once reserved for men, it is now commonly performed in women as well (Stein et al, 1997). Women with bladder cancer whose tumors are not located at the bladder neck and have a clear urethral margin at the time of cystectomy are candidates for this procedure. Approximately 66% of women undergoing radical cystectomy for the management of bladder cancer fall into this group (Stein et al, 1995, 1998a; Stenzl et al, 1995). Intraoperative inspection and frozen-section assessment of the bladder neck limit the risk of urethral recurrence.

The bowel segments should be opened and refashioned (detubularized) to interrupt the normal high-pressure contractions of the intact intestine (Hinman, 1988). A large radius is preferred, as this results in a reservoir with a larger geometric capacity and lower pressure. Continent reservoirs and bladder substitutes of small intestine, large intestine, or a combination of both may be performed. Even though bladder substitution is perceived by some as a more complex procedure, prior studies have demonstrated complication and reoperation rates similar to those for ileal conduit urinary diversion in the hands of experienced surgeons (Gburek et al, 1998; Parekh et al, 2000). Long-term results of bladder replacement demonstrate excellent functional outcomes (Abol-Enein and Ghoneim, 2001; Elmajian et al, 1996; Hautmann et al, 1999; Stein et al, 1997; Stenzl et al, 2001; Steven and Poulsen, 2000). Daytime continence can be expected in 87–100% of men and 82–100% of women. Nighttime continence is achieved in 86–94% of men and 72–82% of women. Nearly all men can void to completion, while approximately 25–50% of women require intermittent catheterization to completely empty the neobladder. It is beyond the scope of this chapter to review all techniques and minor modifications; instead, the most common techniques and the general principles of continent diversion are reviewed.

Ureterosigmoidostomy

The first direct anastomosis of the ureters into the intact colon was performed by Smith in 1878 (Smith, 1879). Peritonitis (from fecal spillage) and pyelonephritis (resulting from ascending infection and stricturing of the ureteral anastomosis) led initially to very high surgical mortality rates. Recognizing that ascending infection from the rectum into the kidney was a major problem, surgeons developed techniques to reimplant the ureters into the colon in an antirefluxing fashion. Since patients will retain large amounts of urine and fecal material simultaneously in the rectum, assurance of adequate rectal sphincter function is important preoperatively. Since ammonia may be absorbed across the bowel surface, patients with liver disease who may be at an increased risk of hyperammonemic encephalopathy should not undergo this procedure. Patients who have primary diseases of the colon or have received extensive pelvic irradiation should undergo alternative forms of diversion.

The ureters are identified at or below the common iliac arteries. The overlying peritoneum is incised, and the ureters are mobilized carefully to preserve their blood supply. A site low in the sigmoid is selected for ureteral reimplantation. The ureters are reimplanted separately into the respective ipsilateral tenia coli, using the antirefluxing techniques described earlier. The peritoneum is sutured over the completed ureteral anastomosis (Figure 23–4).



▲ **Figure 23–4.** Ureterosigmoidostomy.

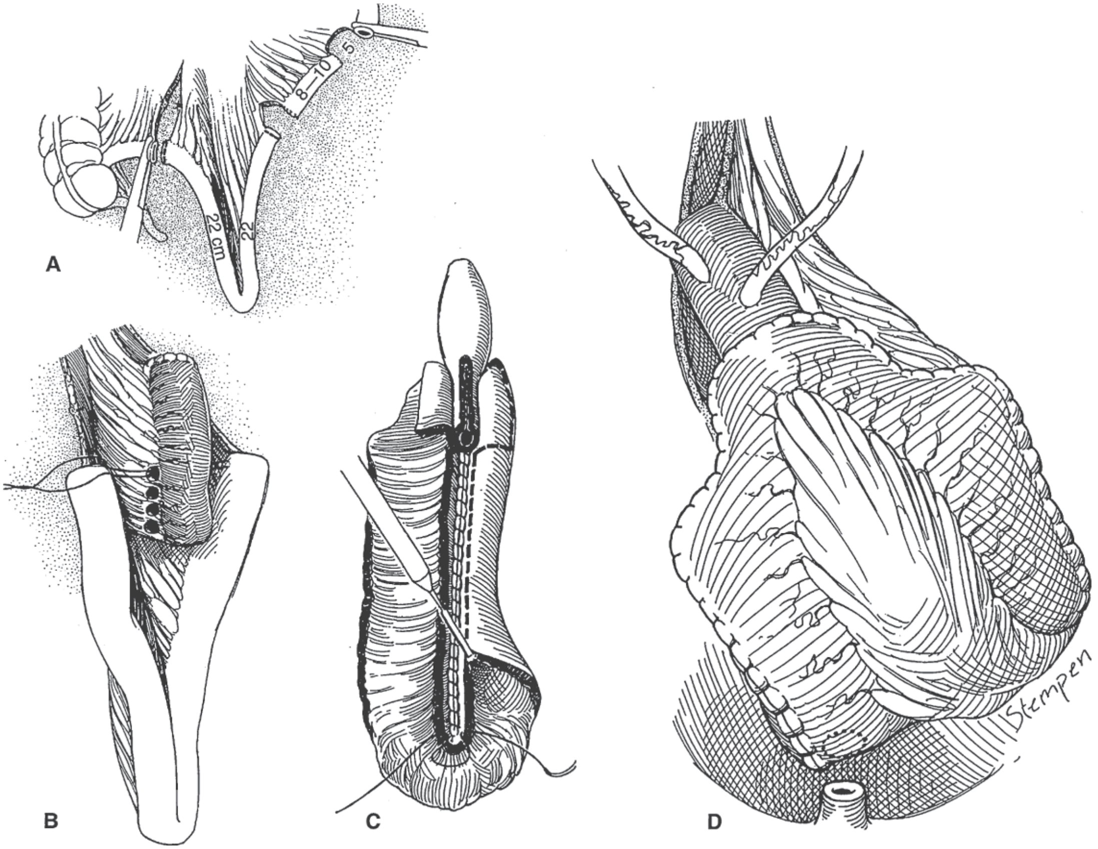
One particularly worrisome complication of ureterosigmoidostomy is development of adenocarcinoma at the site where the ureters have been reimplanted into the large intestine. The incidence of anastomosis site adenocarcinoma is uncertain, but there seems to be a several-thousand-fold increase in its incidence in patients who have undergone ureterosigmoidostomy over individuals who have not undergone this type of surgery. The induction period varies but may be approximately 20 years; thus, the risk is especially high in young patients. Experimental studies have shown that the development of adenocarcinoma seems dependent on the presence of urine, feces, urothelium, and colonic epithelium in close approximation. All those who undergo ureterosigmoidostomy should be counseled to undergo yearly sigmoidoscopy starting 5 years after the procedure and at any time if occult or gross gastrointestinal bleeding or a major change in bowel habits is noted.

Reservoirs Constructed of Small Intestine

Nils Kock was responsible for the early and ongoing development of a continent urinary reservoir fashioned entirely of small intestine (Kock et al, 1982; Nieh, 1997). This reservoir includes the construction of nipple valves as the proximal and distal ends of the reservoir to prevent ureteric reflux (proximally) and incontinence (distally). The Koch reservoir is no longer commonly used because there is a high incidence of complications related to the nipple valves.

To decrease the complication rate associated with the afferent intussuscepted antireflux nipple of the Kock ileal neobladder, Stein and colleagues (1998) described an innovative antireflux technique (Figure 23–5). This new reservoir, the T pouch, has several important advantages over the Kock ileal neobladder: (1) it requires a smaller segment of ileum to create the antireflux technique, (2) the serosal-lined antireflux mechanism eliminates the need for intussusception, (3) blood supply is better preserved, and (4) urine is not in contact with the implanted portion of the ileum.

Camey described a technique of bladder substitution whereby an intact segment of ileum was anastomosed directly to the urethra (Lilien and Camey, 1984). A 40-cm segment of ileum was isolated from the gastrointestinal tract,

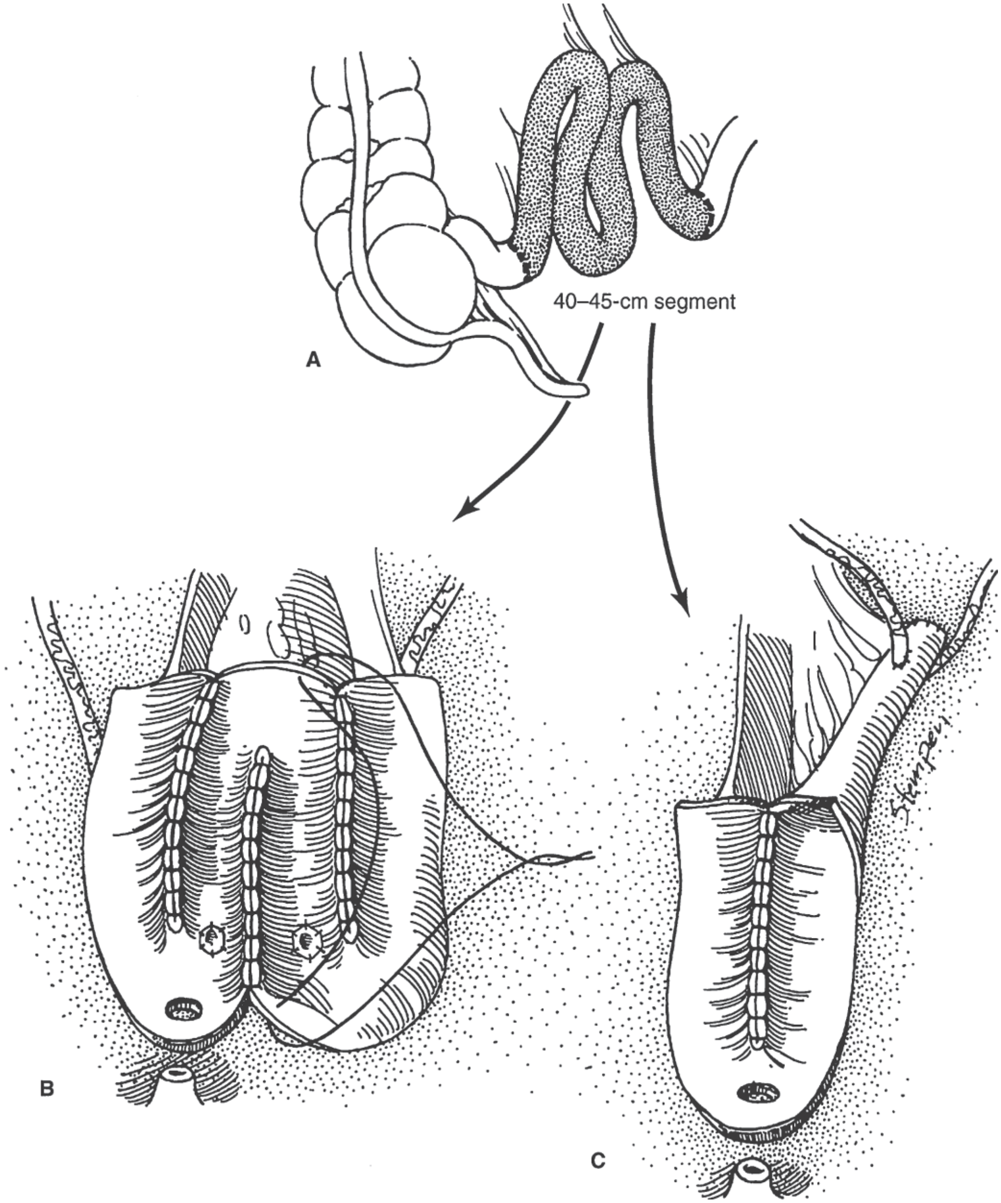


▲ **Figure 23–5.** Construction of a T pouch. ***A:*** Two segments of small intestine are isolated; one portion will form the reservoir, and the smaller, more proximal portion will form the antireflux segment. ***B:*** The longer reservoir portion of the segments is folded into a V configuration. The smaller, antireflux segment is fixed to the serosa of the reservoir portion. ***C:*** The antireflux segment has been opened and tapered with a stapling device. The ileal segments selected for the reservoir portion of the pouch are joined anteriorly and then opened, exposing the mucosa. As the opening reaches the ostium of the antireflux segment, the incisions are carried laterally and create wide flaps that can then be closed over the ostium to cover the tapered antireflux segment. ***D:*** The reservoir portion is closed.

and its midpoint was anastomosed, without tension, directly to the urethra. The ureters were reimplanted into either end of the ileal segment in an antirefluxing fashion. However, failure to detubularize the ileal segment led to a high incidence of urinary incontinence compared with substitutes fashioned from detubularized small-bowel segments (Hautmann et al, 1999; Studer and Zingg, 1997). As illustrated in Figure 23–6, 40–60-cm segments of ileum can be detubularized and folded into U-, S-, or W-shaped reservoirs, which can be connected directly to the urethra. The ureters are reimplanted directly into a short segment of ileum at the proximal end of the bowel segment, isolated to fashion the diversion, which is not detubularized. End-to-side ureteric anastomosis into this isoperistaltic segment of ileum prevents reflux. With the Hautmann type of ileal neobladder (W configuration), nondetubularized segments of ileum can be left intact at either end of the W and the ureters individually implanted into each of these segments. This would make it easier to dissect the ureter if a nephroureterectomy is required at a later date for upper tract tumor recurrence. The larger diameter and lower pressure of these reservoirs compared with those of nondetubularized bowel have led to better continence rates.

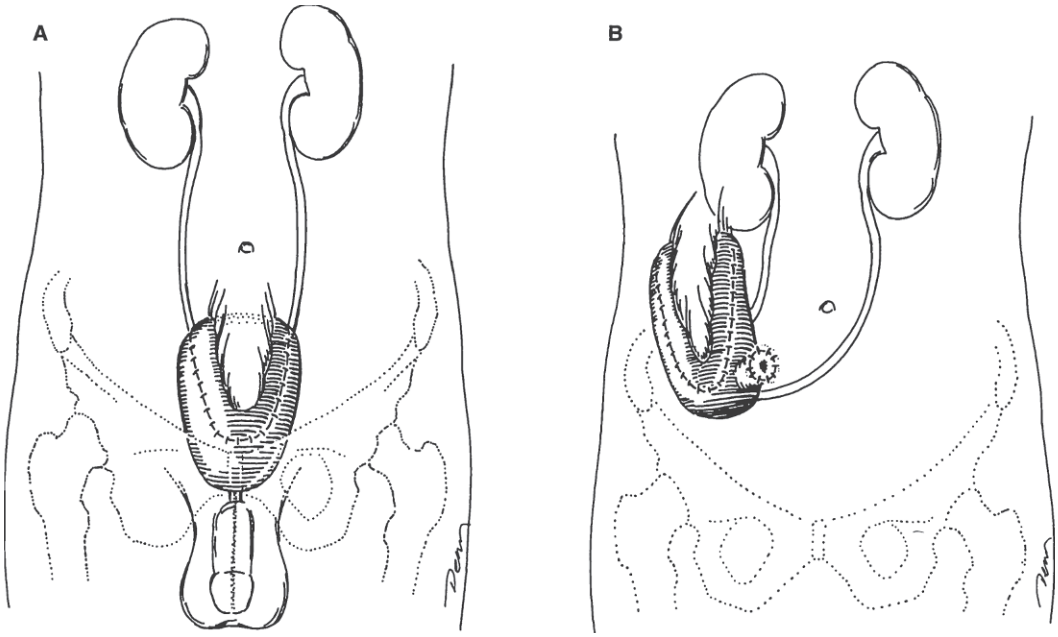
▶ Reservoirs Constructed of Large Intestine

Various investigators have described using segments of the large intestine alone or combinations of large- and small-bowel segments to fashion urinary reservoirs (Bihrle, 1997; Lampel et al, 1996). Bladder substitutes have been constructed using detubularized bowel segments from the



▲ **Figure 23–6.** Bladder substitutes constructed entirely of small intestine. ***A:*** First, 40–45 cm of small intestine is selected. ***B:*** Small intestine is opened and fashioned into a W configuration. The ureters are reimplanted into the second and third limbs of the reservoir, and the reservoir is attached to the urethra. ***C:*** Small intestine is folded into a J configuration with the most proximal portion of the segment remaining unopened. The ureters are reimplanted into the intact ileal segment of the reservoir, and the reservoir is attached to the urethra.

ileocecal region or sigmoid colon. Use of the ascending colon and terminal ileum to construct continent urinary reservoirs has gained great popularity. Cecum and ascending colon are detubularized and refashioned or augmented with the small intestine to provide for a spherical reservoir. The ureters are reimplanted in a nonrefluxing fashion (Figure 23–7). The reservoir can be anastomosed directly to the urethra. In women or in men who require a urethrectomy, a continent,



▲ **Figure 23–7.** Use of the ileocecal segment to construct *(**A**)* a bladder substitute attached to the urethra or *(**B**)* a continent urinary reservoir placed in the abdomen using plicated terminal ileum as a stoma.

catheterizable stoma can be fashioned of appendix or tapered terminal ileum (Figure 23–8).

Postoperative Care

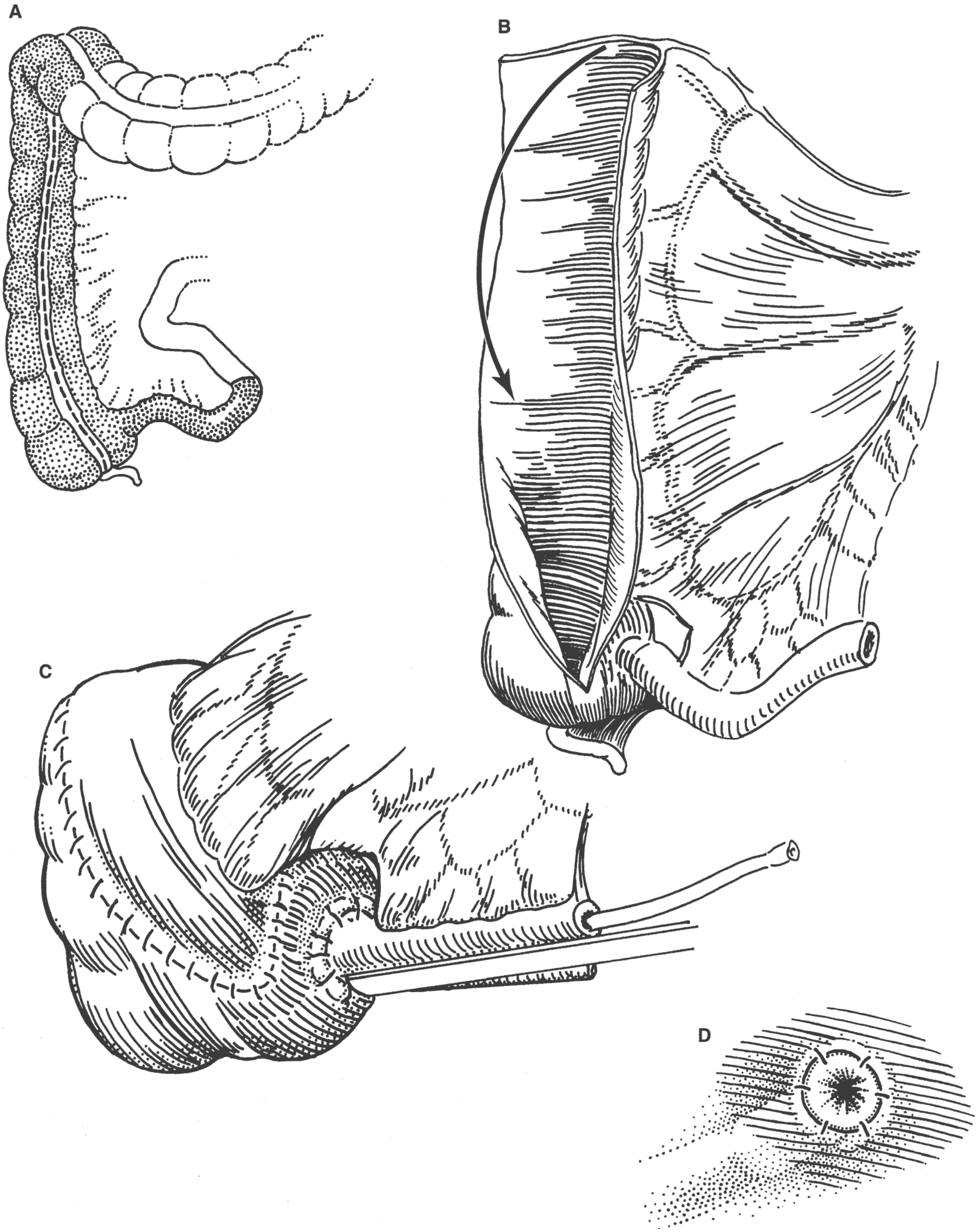
Postoperative care varies depending on the method of urinary diversion or bladder substitution. As with all patients who have undergone major abdominal surgery, early ambulation, use of intermittent compression stockings, and incentive spirometry may be used to prevent pulmonary emboli and respiratory complications. Nasogastric tubes are not routinely necessary but may be used in patients with abdominal distension, nausea, and emesis. Serum electrolytes and creatinine should be monitored postoperatively for the development of metabolic abnormalities. If single-J ureteral stents have been placed, they are usually removed after postoperative day 5; double J stents stay in place for up to 2–3 weeks in patients undergoing neobladders. Continent urinary reservoirs and bladder substitutes produce mucus and thus are irrigated regularly in the early postoperative period to prevent mucus accumulation. Mucus production decreases over time, and irrigation ultimately becomes unnecessary. Upper urinary tract surveillance for hydronephrosis should be performed on a regular basis using ultrasound or computed tomography. An initial assessment of the upper urinary tract is made in the early postoperative period; if upper urinary tract dilation is not found, the patient undergoes repeat imaging on a yearly basis or as dictated by surveillance protocols for the stage of bladder cancer.

COMPLICATIONS

Complications occurring after urinary diversion, bladder substitution, or continent urinary diversion are generally a product of surgical technique, the underlying disease process and its treatment, the age of the patient, and the length of follow-up (Carlin et al, 1997; Gburek et al, 1998). Early complications, which are uncommon (occurring in approximately 10–20% of patients), include excessive bleeding, intestinal obstruction/ileus, urinary extravasation, and infection. Late complications (10–20% of patients) include metabolic disorders, stomal problems (stenosis or hernia), pyelonephritis, and calculi. Rarely, spontaneous neobladder rupture may occur presumably as a result of overdistention or blunt abdominal trauma (Nippgen et al, 2001). Such patients usually present with peritonitis and acute abdominal pain. Perforation of continent cutaneous diversions can occur and can be related to vigorous catheterization.

Metabolic and Nutritional Disorders

Fluid, electrolyte, nutrient, and waste product excretion or absorption normally occurs across the intestinal wall. Metabolic abnormalities may occur when intestinal segments are interposed into the urinary tract. As pointed out previously, use of the jejunum may result in hyponatremic, hypochloremic, or hyperkalemic metabolic acidosis in up to 40% of patients. The jejunum is unable to maintain large solute



▲ **Figure 23–8.** ***A:*** Continent urinary reservoir constructed from the ileocecal segment. ***B:*** Bowel detubularized. ***C:*** Stoma constructed by tapering the terminal ileum with intestinal stapling instrument or sutures. ***D:*** Completed stoma.

gradients, so large amounts of water and solute pass through the jejunal wall. Sodium and chloride are rapidly excreted into the conduit, and potassium is passively absorbed. Aldosterone is produced, resulting in reabsorption of hydrogen and excretion of potassium into the distal tubule of the kidney and consequent acidosis and movement of potassium from the body's intracellular stores. As water is lost into the conduit, extracellular fluid volume is reduced, as is the glomerular filtration rate. The renin–angiotensin system is activated, which further stimulates aldosterone secretion. Urea may be absorbed from the jejunal lumen, which (with dehydration) contributes to azotemia. This syndrome is often characterized clinically by nausea, vomiting, anorexia, and muscle weakness.

The pathogenesis and nature of metabolic abnormalities occurring after incorporation of the ileum or colon into the urinary tract differ from those associated with jejunal conduits. When such segments are used, sodium and chloride are absorbed across the bowel surface. Chloride is absorbed in slight excess of sodium, resulting in a net loss of bicarbonate into the bowel lumen. Preexisting renal failure contributes to the development and severity of the disorder, as does a large bowel surface area and long contact time. Hyperchloremic acidosis is more common in patients who undergo ureterosigmoidostomy than in patients who undergo simple conduit construction using either the ileum or the colon, because of the larger surface area and longer contact time with urine associated with ureterosigmoidostomies. Hyperchloremic metabolic acidosis may manifest clinically as weakness, anorexia, vomiting, Kussmaul breathing, and coma. One potential long-term complication of chronic acidosis may be decreased bone calcium content and osteomalacia (Kawakita et al, 1996; McDougal et al, 1988).

Bile salts are important for fat digestion and uptake of vitamins A and D. Bile salt metabolism may be altered after ileal resection (Olofsson et al, 1998). Resection of small segments of the ileum may be associated with mild malabsorption and steatorrhea owing to increased concentrations of bile salts delivered to the colon. The increased concentration of such salts leads to decreased colonic absorption of water and electrolytes. Resection of large segments of ileum may reduce bile salt reabsorption to very low levels, leading to severe fat malabsorption. Bowel transit time may be reduced further by resection of the ileocecal valve. Cholestyramine may be used to treat secretory bile salt diarrhea. If diarrhea persists, addition of agents such as loperamide that decrease bowel motility and increase transit time may be effective. Cholelithiasis may be more common after ileal resections as well.

Vitamin B_{12} deficiency may occur as a result of either gastric or ileal resection (Fujisawa et al, 2000; Terai et al, 1997). Because B_{12} stores last for years, its deficiency may not become apparent for several years after intestinal surgery. Vitamin B_{12} deficiency results in megaloblastic anemia and peripheral nerve paresthesia. The levels of this vitamin can be assessed in patients after ileal or gastric resection. Alternatively, yearly replacement by injection of vitamin B_{12} is adequate in those in whom deficiency is noted.

Stoma

A substantial amount of patients' dissatisfaction with urinary diversion can be attributed to stomal complications. Stoma construction is especially important in procedures in which a pouch must be worn. Careful stomal construction as outlined earlier is essential (Fitzgerald et al, 1997). Most peristomal skin problems can be avoided with adequate siting, good surgical technique coupled with regular follow-up by a nurse specialized in ostomy care (Enterostomal Therapy Nurse; wound, ostomy, and continence nurse [WOCN]). Complications related to the stoma can be separated into (1) **stomal** complications—necrosis, stenosis, hernia, retraction, or prolapse and (2) **peristomal** complications—dermatitis related to fungal infections, contact allergic reactions, mechanical trauma, and contact dermatitis leading to alkaline encrustations from urine on the skin over time. They are often related, as a stenotic stoma may be difficult to pouch leading to chronic skin irritation. External stomal and peristomal complications rates range from 15% to 65% (Szymanski et al, 2010). The likelihood of stomal stenosis increases with time. Stomal stenosis can lead to conduit elongation and upper-tract obstruction. This condition can be diagnosed relatively easily by catheterizing the stoma and measuring the residual urine volume. It is corrected by revision of the stoma. Parastomal herniation tends to occur as a delayed complication in 5–28% of patients (Franks and Hrebinko, 2001; Szymanski et al, 2010). One cause for this is the location of the stoma lateral to the rectus muscle, which eliminates the circumferential support provided by the muscle cuff around the stoma. The hernia typically tends to occur around the superolateral aspect of the stoma. Placing the stoma such that the conduit is traversing the rectus muscle does not eliminate the risk of parastomal hernia (Gray et al, 2005). Some degree of stomal bulge without a hernia is commonly noted. Repair of a stomal hernia requires reinforcing the rectus fascia with mesh, either intraperitoneally through the previous midline incision or through an incision lateral to the stoma. In some cases, it may be necessary to move the stoma to a new site, preferably to the contralateral side of the abdominal wall. Recurrence rates following hernia repair were high previously but have declined considerably to 0–7% in recent series (Franks and Hrebinko, 2001; Ho and Fawcett, 2004).

Skin irritation or infections are most common in procedures in which an appliance is worn and when there is prolonged contact of the skin with urine. Some patients' skin may be sensitive to adhesive agents.

Stomal or skin problems are minimized by selecting an appropriate pouching system. Extended-wear pouches provide better skin protection because of better adhesion and delayed moisture absorption (Colwell, 2005). The treatment of parastomal conditions is summarized in Table 23-1.

Table 23–1. Common peristomal skin problems and their management.

Problem/Description	Cause	Management
Fungal infections/yeast dermatitis • Usually confluent circumferential rash (fine papules and pustules) with satellite lesions. May be pruritic	• Yeast overgrowth on skin exposed to excess moisture (barrier opening too large, pouch leakage)	• Antifungal powder (Nystatin) or systemic therapy with fluconazole (Diflucan)
Allergic contact dermatitis • Area of erythema, pruritus, and/or blistering that corresponds to allergen	• Allergic reaction in sensitive patient • Once allergic reaction is chronic, it is more difficult to treat and identify irritant	• Identify irritant (skin patch test) and discontinue product • Apply hydrocortisone cream for short period to reduce skin reaction • Topical antihistamines (diphenhydramine gel) • Avoid solvents and soaps under pouch
Mechanical trauma • Denuded peristomal skin without rash or pruritus	• Frequent or excessive pouch changing leading to skin stripping • Pressure trauma from belt or convexity • Overuse of tape around the barrier	• Minimize pouch changes • Encourage gentle skin care or use of protective sealant • Consider nonadhesive pouches (used with belt)
Pseudoverrucous skin lesions • Warty raised macerated lesions around the stoma. May cause bleeding and pain • Late complication	• Urine contact with peristomal skin over extended period • As the lesions develop, patients often keep making the opening larger, compounding the problem	• Ensure correct opening in pouch • Patient will need to cover lesions initially for resolution, and they will need to change their pouch more frequently until the lesions have resolved
Peristomal hernia • Reducible bulge under or around stoma	• Not clear at this time—may be related to abdominal aperture size created at the time of surgery • May be avoided by placing stoma within rectus abdominis sheath	• Flexible pouching system • Surgical repair with mesh or re-siting (tends to recur) • Hernia support belt applied while hernia is reduced (Nu-Hope)
Alkaline encrustation	• Crystal deposits on exposed peristomal skin	• Increase oral fluid intake • Acidify urine with 1 g ascorbic acid daily • 20-minute vinegar soaks at the time of pouch change

Note: The patient should see a wound, ostomy, and continence nurse (WOCN), if available.

The most troublesome stomal complication of external urinary appliances is unexpected pouch leakage. This is often a result of improper application of the pouch but may be caused by poor stomal construction. With a properly constructed and located stoma, the choice of the pouch is relatively simple and is often determined by patient preference. Factors to consider when selecting a pouch include patient dexterity, available resources, and stomal construction. Pouches have an adhesive skin barrier that attaches to the skin and a bag that collects urine. An opening is made in the middle of the skin barrier; this opening should be of a diameter just larger than the stoma to avoid erosion of the stoma or prolonged contact of the skin with urine, typically 0.125 in on each side. However, if the stoma is retracted or at skin level, then the opening may be made more secure if there is 0.25th-inch clearance on each side to avoid undermining (Doughty, 2005).

Most patients favor using disposable urinary collection pouches. Disposable, one-piece pouches are single-use. Two-piece systems allow the patient to remove the pouch, leaving the skin barrier intact. A larger collection device is often attached to the pouch at night.

Continence and Urinary Function

One common late complication of continent urinary diversion is urinary incontinence that can occur following both cutaneous diversion and neobladders. Nighttime incontinence is particularly a problem with neobladders and can occur in about 20–50% of all patients (Lee et al, 2003; Meyer et al, 2004). Daytime incontinence is significantly lower and ranges from <10% to 33%. Reported continence rates are higher with the T pouch at around 87% (daytime) and 72% (nighttime) (Stein, 2004). The wide variations in reported continence rates stem from varying definitions of continence. Improvement in continence is observed with time and increasing neobladder capacity reaching 92% for daytime and 80% at nighttime by 2 years (Studer, 1996). Bladder capacity increases gradually and stabilizes to reach >450 mL, and continence also improves over time in these patients (Permenis, 2004). Incomplete emptying can occur in a small percentage of patients requiring long-term self-catheterization. Women who undergo neobladder construction are especially at risk for hypercontinence, which can occur in 12% to as many as 60% of patients and must be counseled preoperatively in this regard (Stein et al, 2009; Stenzl et al, 2001). Day- and nighttime continence rates appear to be similar between male and female patients and the most common types of neobladders reconstruction (Studer vs Hautmann) (Lee et al, 2003; Stenzl et al, 2001). Sphincteric damage and low urethral resting pressures are believed to be the reasons for incontinence while urethral denervation, poor pouch contractility, and/or exaggerated acute angulation of the neobladder urethral junction are believed to be the reasons for hypercontinence and retention. Frequent bladder emptying, urethral collagen injection, artificial urinary sphincter placements, and urethral slings are all potential treatment options for incontinence while catheterization is the main therapy for urinary retention.

Pyelonephritis and Renal Deterioration

Pyelonephritis occurs in approximately 10% of patients who have undergone urinary diversion. Treatment is based on a properly collected urine sample for culture. A urine sample should not be collected from the pouch; rather, the pouch should be removed, the stoma cleansed with an antiseptic, and a catheter advanced gently through the stoma. If infection has occurred in a patient with a simple conduit, the volume of residual urine within the conduit should be recorded. Obstruction and stasis of urine within the reconstructed urinary tract are risk factors for the development of infection.

Although many patients with preexisting dilation of the upper urinary tract show improvement or resolution of the dilation after urinary diversion or bladder substitution, progressive renal deterioration as manifest by hydronephrosis, and/or an increasing serum creatinine level occurs in some patients who undergo these procedures. The incidence of either complication increases after 10 years. The presence of hydronephrosis, particularly in patients with a conduit diversion, may indicate the presence of ureteric reflux or obstruction at the ureteral anastomosis. A loopogram can help demonstrate whether there is retrograde flow of contrast from conduit to the ureter and renal pelvis. In some situations, it may be necessary to obtain a radionuclide renal scan (MAG3) to assess the antegrade flow of urine from the kidney through the ureters. Pyelographic evidence of upper urinary tract deterioration has been noted in up to 50% of patients who have undergone urinary diversion at an early age. Recurrent upper urinary tract infection and high-pressure ureteral reflux and obstruction, usually in combination, contribute to the likelihood of renal deterioration. Upper tract deterioration is less likely following ileal continent diversion. While most kidneys will demonstrate mild dilation, 97% of patients show no change in renal parenchymal size and 100% show no change in serum creatinine 10–15 years following the Studer type of ileal neobladder (Perimenis, 2004).

Calculi

Calculi occur in approximately 8% of patients who undergo urinary diversion or bladder substitution (Cohen and Streem, 1994; Terai et al, 1996). Such patients have several risk factors for the development of various calculi. Nonabsorbable staples, mesh, or suture material used to construct conduits or reservoirs may act as a nidus for stone formation. Colonization in either conduits or reservoirs is common, whereas symptomatic infection is much rare. Certain bacteria can contribute to stone formation; some bacteria commonly found in the urinary tract, including *Proteus*, *Klebsiella*, and *Pseudomonas* species, produce urease, a urea-splitting enzyme that contributes to the formation of ammonia and carbon dioxide. Hydrolysis of these products results in an alkaline urine supersaturated with magnesium ammonium phosphate, calcium phosphate, and carbonate apatite crystals. Management of such infection-related stones requires stone removal, resolution of infection, and, often, use of adjunctive agents to complete stone dissolution.

The likelihood of stone formation is increased by the development of systemic acidosis. Prolonged contact of the urine with the intestinal surface facilitates the exchange of chloride for bicarbonate. Bicarbonate loss results in systemic acidosis and hypercalciuria. The combination of hypercalciuria and alkaline urine predisposes a patient to the development of calcium calculi. In addition, the terminal ileum is responsible for bile salt absorption; if this portion of the intestine is used for conduit or bladder reservoir construction, excess bile salts in the intestine may bind calcium and result in increased absorption of oxalate, which may lead to the development of oxalate-containing calculi. Hypocitraturia may also be a risk factor for stone disease in patients undergoing bladder replacement (Osther et al, 2000). Excess conduit length, urine stasis, and dehydration make the development of calculi more likely.

BIBLIOGRAPHY

Abol-Enein H, Ghoneim MA: Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: Experience with 450 patients. J Urol 2001;165:1427.

Allareddy V et al: Quality of life in long term bladder cancer survivors. Cancer 2006;106:2355.

Bass EM et al: Does preoperative stoma marking and education by the enterostomal therapist affect outcomes? Dis Colon Rectum 1997;40:440.

Bihrle R: The Indiana pouch continent urinary reservoir. Urol Clin North Am 1997;24:773.

Bjerre BD et al: Health-related quality of life after cystectomy: Bladder substitution compared with ileal conduit diversion. A questionnaire survey. Br J Urol 1995;75:200.

Carlin BI et al: Comparison of the ileal conduit to the continent cutaneous diversion and orthotopic neobladder in patients undergoing cystectomy: A critical analysis and review of the literature. Semin Urol Oncol 1997;15:189.

Carlin BI et al: Comparison of the ileal conduit to the continent cutaneous diversion and orthotopic neobladder in patients undergoing cystectomy: A critical analysis and review of the literature. Semin Urol Oncol 1997;15:189.

Cohen T, Streem S: Minimally invasive endourologic management of calculi in continent urinary reservoirs. Urology 1994;43:865.

Colwell JC, Fichera A: Care of the obese patient with an ostomy. J Wound Ostomy Continence Nurs 2005;32:378.

Colwell JC: Dealing with ostomies: Good care, good devices, good quality of life. J Support Oncol 2005;3:72.

Doughty D: Principles of ostomy management in the oncology patient. J Support Oncol 2005;3:59.

Dutta SC et al: Health-related quality of life assessment after radical cystectomy: Comparison of ileal conduit with continent orthotopic neobladder. J Urol 2002;168:164.

Elmajian DA et al: The Kock ileal neobladder: updated experience in 295 male patients. J Urol. 1996 ;156:920–925.

Fitzgerald J et al: Stomal construction, complications, and reconstruction. Urol Clin North Am 1997;24:729.

Fitzgerald J et al: Stomal construction, complications, and reconstruction. Urol Clin North Am 1997;24:729.

Franks ME, Hrebinko RL Jr: Technique of parastomal hernia repair using synthetic mesh. Urology 2001;57:551.

Fujisawa M et al: Health-related quality of life with orthotopic neo-bladder versus ileal conduit according to the SF-36 survey. Urology 2000;55:862.

Fujisawa M et al: Long-term assessment of serum vitamin B_{12} concentrations in patients with various types of orthotopic intestinal neobladder. Urology 2000;56:236.

Gburek BM et al: Comparison of the Studer ileal neobladder and ileal conduit urinary diversion with respect to perioperative outcome and late complications. J Urol 1998;160:721.

Gburek B et al: Comparison of Studer ileal neobladder and ileal conduit urinary diversion with respect to perioperative outcome and late complications. J Urol 1998;160:721.

Gilbert SM et al: Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI). Cancer 2007;109:1756–1762.

Gray M et al: What treatments are effective for the management of peristomal hernia? J Wound Ostomy Continence Nurs 2005;32:87.

Hara I et al: Health-related quality of life after radical cystectomy for bladder cancer: A comparison of ileal conduit and orthotopic bladder replacement. BJU Int 2002;89:10.

Hautmann R et al: The ileal neobladder: Complications and functional results in 363 patients after 11 years of followup. J Urol 1999; 161:422.

Hinman F Jr: Selection of intestinal segments for bladder substitution: physical and physiological characteristics. J Urol 1988; 139:519–523.

Ho KM, Fawcett DP: Parastomal hernia repair using the lateral approach. BJU Int 2004;94:598.

Iselin C et al: Does prostate transitional cell carcinoma preclude orthotopic bladder reconstruction after radical cystoprostatectomy for bladder cancer? J Urol 1997;158:2123.

Kawakita M et al: Bone demineralization following urinary intestinal diversion assessed by urinary Pyridium cross-links and dual energy x-ray absorptiometry. J Urol 1996;156:355.

Kock NG et al: Urinary diversion via a continent ileal reservoir: Clinical results in 12 patients. J Urol 1982;128:469.

Lampel A et al: Continent diversion with the Mainz pouch. World J Urol 1996;14:85.

Lee KS et al: Hautmann and Studer orthotopic neobladders: A contemporary experience. J Urol 2003;169:2188.

Lilien OM, Camey M: 25-year experience with replacement of the human bladder (Camey procedure). J Urol 1984;132:886.

McDougal WS et al: Boney demineralization following intestinal diversion. J Urol 1988;140:853.

Meyer JP et al: A three-centre experience of orthotopic neobladder reconstruction after radical cystectomy: Initial results. BJU Int 2004;94:1317.

Nelson RL et al: Antimicrobial prophylaxis for colorectal surgery. Cochrane Database Syst Rev 2009;21(1):CD001181.

Nelson RL et al: Antimicrobial prophylaxis for colorectal surgery. Cochrane Database Syst Rev 2009;21(1):CD001181.

Nieh P: The Kock pouch urinary reservoir. Urol Clin North Am 1997;24:755.

Nippgen JBW et al: Spontaneous late rupture of orthotopic detubularized ileal neobladders: Report of five cases. Urology 2001; 58:43.

Nixon RG et al: Carcinoma in situ and tumor multifocality predict the risk of prostatic urethral involvement at radical cystectomy in men with transitional cell carcinoma of the bladder. J Urol 2002;167:502.

Okada Y et al: Quality of life survey of urinary diversion patients: Comparison of continent urinary diversion versus ileal conduit. Int J Urol 1997;4:26.

Olofsson G et al: Bile acid malabsorption after continent urinary diversion with an ileal reservoir. J Urol 1998;160:724.

Osther PJ et al: Stone risk after bladder substitution with the ileal-urethral Kock reservoir. Scand J Urol Nephrol 2000;34:257.

Parekh DJ et al: Continent urinary reconstruction versus ileal conduit: A contemporary single-institution comparison of perioperative morbidity and mortality. Urology 2000;55:852.

Perimenis P et al: Ileal orthotopic bladder substitute combined with an afferent tubular segment: Long-term upper urinary tract changes and voiding pattern. Eur Urol 2004;46:604.

Richie JP: Sigmoid conduit urinary diversion. Urol Clin North Am 1986;13:225.

Richie JP et al: Urinary diversion: The physiological rationale for non-refluxing colonic conduits. Br J Urol. 1975;47(3):269–275.

Slim K et al: Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg 2009;249:203–209.

Slim K et al: Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg 2009;249:203–209.

Smith T: An account of an unsuccessful attempt to treat extroversion of the bladder by a new operation. St Barth Hosp Rep 1879;15:29.

Stein JP et al: Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: A pathological review of female cystectomy specimens [see comments]. J Urol 1995;154:1329.

Stein JP et al: Long term oncological outcome in women undergoing radical cystectomy and orthotopic diversion for bladder cancer. J Urol 2009;181:2052–2059.

Stein JP et al: The orthotopic T pouch ileal neobladder: Experience with 209 patients. J Urol 2004;172:584.

Stein J et al: Orthotopic lower urinary tract reconstruction in women using the Kock ileal neobladder: Updated experience in 34 patients. J Urol 1997;158:400.

Stein J et al: Prospective pathologic analysis of female cystectomy specimens: Risk factors for orthotopic diversion in women. Urology 1998a;51:951.

Stein J et al: The T pouch: An orthotopic ileal neobladder incorporating a serosal lined ileal antireflux technique. J Urol 1998b;159:1836.

Stein R et al: Long-term metabolic effects in patients with urinary diversion. World J Urol 1998;16:292.

Stenzl A et al: The risk of urethral tumors in female bladder cancer: Can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol 1995;153(3 Pt 2):950.

Stenzl A et al: Urethra-sparing cystectomy and orthotopic urinary diversion in women with malignant pelvic tumors. Cancer 2001; 92:1864.

Stenzl A et al: Urethra-sparing cystectomy and orthotopic urinary diversion in women with malignant pelvic tumors. Cancer 2001;92:1864.

Steven K, Poulsen AL: The orthotopic Kock ileal neobladder: Functional results, urodynamic features, complications, and survival in 166 men. J Urol 2000;164:288.

Studer UE et al: Summary of 10 years' experience with an ileal low-pressure bladder substitute combined with an afferent tubular isoperistaltic segment. World J Urol 1996;14:29.

Studer U, Zingg E: Ileal orthotopic bladder substitutes. Urol Clin North Am 1997;24:781.

Szymanski KM et al: External stoma and peristomal complications following radical cystectomy and ileal conduit diversion: A systematic review. Ostomy Wound Manage 2010;1:28.

Terai A et al: Urinary calculi as a late complication of the Indiana continent urinary diversion: Comparison with the Kock pouch procedure. J Urol 1996;155:66.

Terai A et al: Vitamin B12 deficiency in patients with urinary intestinal diversion. Int J Urol. 1997;4:21–25.

This page intentionally left blank

Systemic Therapy of Urologic Tumors

24

Vadim S. Koshkin, MD; & Eric J. Small, MD

The use of chemotherapy, targeted therapeutics, and more recently immunotherapy (see Chapter 25) in the treatment of malignant tumors of the genitourinary system serves as a paradigm for a multidisciplinary approach to cancer. The careful integration of surgical and systemic treatments has resulted in impressive advances in the management of urologic cancers. By definition, surgical interventions are directed at local management of urologic tumors, whereas chemotherapy and biologic therapy are systemic in nature. Although there is no question that there are times in the natural history of a genitourinary tumor when only one therapeutic method is required, a multidisciplinary approach is usually beneficial. This chapter details the importance of a joint surgical–medical approach to patients with urologic malignancies. A practicing urologist should collaborate closely with a medical oncologist and should feel comfortable speaking with patients about the uses, risks, and benefits of chemotherapy, and other forms of systemic therapy such as tyrosine kinase inhibitors (TKIs) or immunotherapy. The role of immunotherapy in the management of genitourinary tumors is covered in Chapter 25.

PRINCIPLES OF SYSTEMIC THERAPY

Clinical Uses

Systemic therapy is indicated in the treatment of disseminated cancer when either cure or palliation is the goal. In addition, systemic therapy may be used as part of a multimodality treatment plan in order to improve both local and distant control of the tumor. An understanding of the goals and limitations of systemic therapy in each of these settings is important for its effective use.

A. Curative Intent for Metastatic Disease

Regarding the role of potentially curative systemic therapy in patients with metastatic disease, several factors must be considered. The first is the responsiveness of the tumor. **Responsiveness** is generally defined by the observed partial or complete responses that together constitute the overall objective response rate. The assessment of neoplasms with frequent bony metastases such as prostate cancer, renal cell carcinoma, and transitional cell carcinoma (TCC) is difficult, as a persistently abnormal bone scan does not necessarily imply residual cancer. Patients in whom the only site of disease is bone generally must be considered nonassessable by conventional measures, and if available, intermediate markers of response (eg, prostate-specific antigen [PSA]) are required. The transient worsening appearance of a bone scan with therapy but that represents healing bone is termed “bone scan flare,” and can be indistinguishable from true disease progression. For this reason, assessment of all parameters including symptomatology, PSA in prostate cancer patients, CT, and MRI is essential. For patients with metastatic prostate cancer in whom bone scan flare is suspected or possible, repeating scans several months later is essential. Increasingly, the ability of an agent to delay objective progression, typically measured as **progression-free survival** (PFS), has been used as an intermediate marker of responsiveness, although there has not always been an association of PFS with overall survival (OS). If cure is the intent with systemic therapy, the relevant response criterion to consider is the percentage of patients achieving a complete response. This number is less than 10% in patients with metastatic renal cell carcinoma and metastatic castration-resistant prostate cancer (mCRPC), 15% or less in patients with metastatic transitional cell carcinoma, and up to 80% in patients with metastatic germ cell malignancies. Under some circumstances, an apparent partial response can be converted into a complete response with judicious surgical resection (eg, in postchemotherapy residual masses in patients with germ cell carcinoma; see Section C below).

The second feature to consider in treating patients with potentially curative systemic therapy is the anticipated toxicity of such therapy. In general, higher levels of toxicity are acceptable if a cure can be achieved, although care must be exercised to avoid a "cure worse than the disease." This is particularly true in the case of fairly toxic therapies such as interleukin 2 (IL2), and high-dose chemotherapy with peripheral stem cell or bone marrow transplantation. These treatments can result in apparent cures of approximately 5–10% and 30%, respectively, of patients with metastatic renal cell carcinoma or refractory germ cell tumors (GCTs). Patients undergoing these rigorous therapies must be carefully selected and must be as fully informed as possible about potential toxicities.

B. Treatment of Patients with Incurable Metastatic Cancer

When the goal of systemic therapy is palliation of symptoms rather than cure, the toxicity of the treatment to be offered must be balanced against the cancer-related symptoms that the patient is experiencing, and in general, more toxic therapies are not indicated. Nonetheless, the potential capabilities of systemic therapy must be understood because even in otherwise incurable disease there may be a role for systemic therapy if there is a likelihood that the patient's life can be prolonged with its use. This is the case for docetaxel or cabazitaxel therapy in mCRPC or combination cisplatinum-based chemotherapy in bladder cancer, and TKIs in renal cell carcinoma. In addition, systemic therapy can be associated with pain control, and an improvement in quality of life. This is the case for docetaxel, cabazitaxel, and mitoxantrone in patients with mCRPC.

C. Systemic Therapy Used in Conjunction with Surgery: Adjuvant and Neoadjuvant Therapy

Systemic therapy administered after a patient has been rendered free of disease surgically is termed **adjuvant therapy**. Several important criteria must be met if adjuvant therapy is to be used outside of a research setting:

1. An assessment must be undertaken of known risk factors predictive of relapse or development of distant metastases. Patients at low risk of relapse generally should not receive adjuvant therapy because they are unlikely to derive a benefit and will be unnecessarily exposed to the toxicity of therapy.
2. The proposed therapy must have been shown to decrease the rate of relapse and increase the disease-free interval (and, it is hoped, survival) in a randomized, phase III trial.
3. Finally, because patients who are being treated with adjuvant therapy are free of disease and presumably asymptomatic, toxicity must be kept at a minimum.

This opens the way to a tailored approach in which patients who undergo primary resection of their cancer, but who are at high risk of harboring micrometastatic disease based on pathologic features of the resected specimen, receive systemic therapy in order to decrease micrometastases and the risk of subsequent recurrence. An example of this approach is the use of adjuvant BEP chemotherapy in high-risk clinical stage I NSGCT, in which patients with lymphovascular invasion, with a 40–60% risk of recurrence, can have the risk of recurrence decreased to 4% or less.

By contrast, **neoadjuvant therapy** is administered before definitive surgical resection. Here, the potential advantages include early therapy of micrometastatic disease and tumor debulking to allow a more complete resection. The best example of highly effective neoadjuvant systemic therapy is the use of platinum-based chemotherapy for patients with muscle-invasive bladder TCC, which has been shown to prolong survival. As with adjuvant therapy, the proposed therapy must have been demonstrated to impact favorably on rate of relapse, disease-free interval, and survival in a randomized phase III trial.

D. Consolidation of Systemic Therapy for Metastatic Disease with Surgery

Patients with known metastatic disease generally do not exhibit sufficiently high response rates to systemic therapy to warrant surgery following chemotherapy, with the clear exception of patients with GCT, where resection of residual masses after chemotherapy is generally warranted. Individual patients with metastatic renal cell carcinoma who exhibit a partial response to systemic therapy, typically with a TKI, may benefit from resection of residual masses, although this approach has not been tested in large trials. This approach is almost never used in patients with metastatic CRPC or TCC.

▶ Systemic Agents and Their Toxicities

The usefulness of antineoplastic agents lies in their therapeutic index or preferential toxicity to malignant cells over normal, nonmalignant cells. The mechanism of action of most chemotherapeutic drugs is based on their toxicity to rapidly dividing cells. Thus, in general, malignancies that have relatively rapid growth, such as GCT, are relatively chemosensitive, whereas slower-growing neoplasms such as renal cell carcinoma are less sensitive to chemotherapy. Toxicity from chemotherapeutic agents is seen primarily in normal, nonmalignant cells that are also rapidly dividing, such as hematopoietic cells in the bone marrow, gastrointestinal mucosa, and hair follicles, and is manifested in cytopenias, mucositis, fatigue, and alopecia. Other common toxicities observed with chemotherapy used in the treatment of genitourinary malignancies include nephrotoxicity, neurotoxicity, hemorrhagic cystitis, pulmonary fibrosis, and cardiotoxicity. TKIs are associated with side effects such as hypertension, nephritis, proteinuria, mucositis, and hand–foot syndrome. Table 24–1 summarizes the spectrum of activity and primary toxicities of commonly used systemic therapeutics.

Table 24–1. Commonly used nonhormonal systemic agents in urologic oncology and their toxicities.[a]

Agent	Activity	Common toxicities
Bleomycin	Germ cell tumors	Fever, chills, pulmonary fibrosis
Cabazitaxel	Prostate cancer	Myelosuppression
Carboplatin	Bladder cancer, germ cell tumors, prostate cancer	Myelosuppression
Cisplatin	Bladder cancer, germ cell tumors, prostate cancer	Renal insufficiency, peripheral neuropathy, auditory toxicity, myelosuppression
Docetaxel (Taxotere)	Prostate cancer, bladder cancer, germ cell tumors	Myelosuppression, neuropathy
Doxorubicin	Bladder cancer, prostate cancer	Myelosuppression, mucositis, cardiomyopathy
Etoposide (VP-16)	Germ cell tumors, prostate cancer	Myelosuppression
Gemcitabine (Gemzar)	Bladder cancer	Myelosuppression
Ifosfamide	Germ cell tumors	Myelosuppression, neurologic (CNS) toxicity, cystitis
Methotrexate	Germ cell tumors, bladder cancer	Mucositis, myelosuppression, renal toxicity
Mitoxantrone	Prostate cancer	Myelosuppression, cardiac toxicity
Paclitaxel (Taxol)	Bladder cancer, germ cell tumors	Myelosuppression, neuropathy
Vinblastine	Bladder cancer, germ cell tumors, prostate cancer	Peripheral neuropathy, autonomic neuropathy; myelosuppression
Tyrosine kinase Inhibitors	Renal cell cancer	Diarrhea, hypertension, fatigue, rash, palmar–plantar erythrodysesthesia (hand–foot syndrome)
Bevacizumab	Renal cell cancer	Hypertension, fatigue, proteinuria
mTOR Inhibitors	Renal cell cancer	Cytopenia, fatigue, stomatitis, diarrhea, pulmonary toxicity

[a]Immunotherapy is considered in Chapter 25.

The development of drug resistance remains an important clinical problem in the field of oncology. Malignant cells develop resistance in a variety of ways, including the induction of transport pumps, which actively pump the drug out of the cell and through increased activity of enzymes necessary to inactivate a specific chemotherapeutic agent. Although there are several experimental methods of circumventing these mechanisms of drug resistance, one practical approach to this problem is the use of multiagent chemotherapy. Increased tumor cell killing is achieved by exposing neoplastic cells to multiple agents with different mechanisms of action. This approach allows the selection of agents with nonoverlapping toxicity profiles, although in general multiagent regimens are more toxic than monotherapy.

The use of increased dose intensity (higher doses of a drug administered over the same time period) as a means of overcoming drug resistance remains experimental in urologic malignancies with one clear exception—a subset of patients with otherwise incurable GCT appear to be curable with high-dose chemotherapy and autologous bone marrow or peripheral stem cell transplant support. While potentially curative, this approach carries considerable toxicity, limiting its use to nonelderly patients without comorbidities.

Unique Features of Genitourinary Malignancies

The systemic therapy of urologic malignancies offers unique challenges to the practitioner. Renal insufficiency due to obstructive uropathy from local extension of the tumor or postsurgical or postradiotherapy changes is not infrequent and may alter antineoplastic drug clearance. In patients with renal cell carcinoma, previous nephrectomy may also impact drug clearance. Furthermore, the common use of the nephrotoxic chemotherapeutic agent cisplatin in the treatment of urologic malignancies (most prominently in bladder and testicular neoplasms) may further diminish renal function. Careful attention must be paid, therefore, to renal function throughout the course of systemic therapy, with appropriate dose adjustments made. TKIs can cause nephritis and proteinuria. Dosing adjustments also must be considered in patients who have undergone cystectomy because ileal conduits or neobladders have the capacity to resorb chemotherapeutic agents that are excreted in the urine in active form (most notably, methotrexate). Frequent local extension in the pelvis presents additional unique problems. Patients with previous pelvic radiotherapy have markedly diminished bone marrow reserves, which may limit the use of myelosuppressive drugs. Furthermore, local pelvic relapses have the potential to be symptomatic and painful. Particularly in patients who have already received radiotherapy, systemic therapy may be important for palliation.

GERM CELL TUMORS (GCT)

Overview

The evolution of therapy for testicular cancer and GCTs has been deliberate and thoughtful and has resulted in cures of 80–85% of men with GCT, serving as a model for the treatment of curable cancers. Nonetheless, challenges in the management of GCT remain. Because of their young age, patients who have been cured are at risk of experiencing delayed, treatment-induced toxicity, including secondary malignancies. Furthermore, an 80–85% cure rate also implies that 15–20% of patients with GCT will not be cured and ultimately will succumb to their disease. An understanding of staging and risk assessment is crucial if patients with (1) good risk features are not to be overtreated and exposed to undue toxic risks, and (2) poor risk features are to receive adequate (curative) therapy.

The most common multiagent chemotherapy regimen for the treatment of GCT is a three-drug combination consisting of bleomycin, etoposide, and cisplatin (BEP). The regimen consists of cisplatinum 20 mg/m^2 IV on days 1–5; etoposide 100 mg/m^2 IV on days 1–5; and bleomycin, 30 units IV, on days 2, 9, and 16. The entire regimen is repeated every 21 days, and each 21-day regimen constitutes one "cycle." The number of cycles that are administered range from 1 (in the stage I adjuvant setting) to 4 (in high-risk stage IV metastatic disease). The omission of bleomycin from this regimen results in the etoposide/cisplatinum (EP) regimen. EP is also given on a 3-week cycle, generally 4 times. The substitution of ifosfamide for bleomycin yields the VIP regimen (VP-16 (etoposide), ifosfamide, cisplatinum).

Use of Chemotherapy for Patients with Stages I and II Disease

The standard of care for patients with stage I GCT remains orchiectomy generally followed by surveillance. In high-risk seminoma patients following orchiectomy, a single dose of adjuvant carboplatin is an option that reduces the risk of recurrence and has been shown to be as effective as retroperitoneal radiation and may be associated with a lower incidence of secondary malignancies, including contralateral testicular neoplasms. In high-risk (vascular invasion) stage I nonseminoma germ cell tumor (NSGCT) patients, one cycle of adjuvant BEP is an option and reduces the risk of recurrence. Similarly, patients with low-volume stage II NSGCT who have undergone retroperitoneal lymphadenectomy may benefit from two cycles of adjuvant EP or cisplatin–etoposide–bleomycin (BEP) chemotherapy. In all low-stage patients, although systemic adjuvant chemotherapy reduces the risk of recurrence, the high efficacy of systemic therapy at recurrence results in similar survival rates regardless of whether adjuvant therapy is used.

Use of Chemotherapy in Patients with Advanced Disease

Patients with advanced GCT should be treated with systemic therapy after completion of their orchiectomy. A variety of chemotherapy regimens will result in over 80% of patients with advanced GCT achieving a complete response and long-term cures. However, around 20% of patients with advanced disease have a poor prognosis and will ultimately die from their disease. Studies of pretreatment clinical characteristics have sought to identify prognostic features that can be prospectively used to segregate this diverse group of advanced GCT patients into poor- and good-prognostic subsets, with the goals of deintensifying therapy in good-risk patients, and treatment intensification poor-risk patients.

A common classification system has been developed by the International Germ Cell Cancer Collaborative Group (IGCCC). In this system, good-prognosis patients with nonseminomatous GCT have a testicular or retroperitoneal primary tumor, no nonpulmonary visceral metastases, and low-serum tumor markers. Intermediate-prognosis patients are the same as good-prognosis patients but have intermediate serum tumor markers. Poor-prognosis patients have a mediastinal primary tumor or nonpulmonary visceral metastases (liver, bone, brain) or high levels of serum tumor markers. The 5-year overall survival rates for the good-, intermediate-, and poor-prognosis categories with current regimens are 92%, 80%, and 48%, respectively. Typically, seminomas are never in the poor-prognosis category. Seminomas are segregated into good-prognosis cases (any primary site, but no nonpulmonary visceral metastases), with an 86% 5-year survival, and intermediate-prognosis cases (any primary site but with the presence of nonpulmonary visceral metastases), with a 72% 5-year survival.

Because the extraordinarily high cure rate for good-prognosis patients is unlikely to improve further, most efforts in the treatment of these patients have been aimed at optimizing treatment with less toxic regimens that will have equal efficacy. Trials evaluating (1) the elimination of bleomycin, (2) a reduction in the number of chemotherapy cycles administered, or (3) the substitution of carboplatin for cisplatin have been undertaken. Acceptable regimens for good-prognosis patients consist of either three cycles of BEP or four cycles of EP.

The outlook for poor-prognosis patients is not as good, and the major objective in poor-prognosis patients has been to improve efficacy, with less concern for reducing toxicity. Four cycles of BEP or four cycles of VIP are appropriate options. The use of paclitaxel containing regimens (TIP) or high-dose chemotherapy with peripheral stem cell transplantation are useful as "salvage" second-line therapy for those patients who progress following standard front-line therapy; their use as primary front-line therapy in high-risk patients is under investigation.

Adjunctive Surgery and "Salvage" Therapy

Postchemotherapy adjunctive surgery must be integrated into the treatment plan of patients with advanced GCT. Approximately 20% of patients with GCTs have residual masses after systemic therapy. Adjunctive surgery usually can be undertaken safely within 1–2 months of completion of chemotherapy. Except in rare circumstances, adjunctive surgery is not indicated in the presence of persistently elevated serum tumor markers. It must be noted, however, that all patients who have received bleomycin, regardless of whether there is clinical evidence of pulmonary fibrosis, are at risk of developing oxygen-related pulmonary toxicity. The anesthesiologist must be made aware of the patient's previous exposure to bleomycin, and every effort must be taken to maintain the **fraction of inspired oxygen (FiO_2)** as low as possible throughout the surgical procedure. Patients who are found to have active carcinoma in their resected specimens are frequently treated with further "salvage" chemotherapy, generally with a different regimen, including the TIP regimen mentioned above. Patients who have undergone postchemotherapy surgical resection who benefit from additional postsurgical chemotherapy are patients with incomplete resections, patients whose resected specimen contains more than 10% viable cancer cells, and patients who were in the IGCCC high-risk group prior to beginning front-line chemotherapy.

In those patients who do not achieve a complete response or who relapse following front-line therapy, second-line therapy is appropriate. Before the initiation of second-line therapy, the diagnosis of relapsed or primary, refractory GCT must be clearly established. In particular, falsely elevated human chorionic gonadotropin or α-fetoprotein values and false-positive radiographic studies of the chest due to previous bleomycin use must be ruled out. Persistent or slowly growing masses, particularly in the absence of serologic progression, may represent benign teratoma. Therapies based on ifosfamide, paclitaxel (eg, the TIP regimen cited above), or high-dose chemotherapy with autologous bone marrow transplant provide a salvage rate of approximately 25% in patients with relapsed or refractory GCT.

UROTHELIAL (TRANSITIONAL CELL) CARCINOMA

Nonmetastatic Disease

The development of effective chemotherapy regimens for the treatment of metastatic transitional cell carcinoma (TCC) has resulted in more widespread use of these regimens in combination with other modalities for the treatment of locally advanced but nonmetastatic disease. In bulky inoperable invasive bladder tumors (T3b, T4, and N+), chemotherapy has been used as a means of cytoreduction in order to enable surgery. Chemotherapy before surgery, termed **neoadjuvant therapy,** has also been used in muscle-invasive cancers that *are* resectable, in order to treat micrometastatic disease prior to cystectomy. The complete pathologic response rate in the bladder after neoadjuvant chemotherapy has been shown to be in the 20–40% range; therefore, definitive surgical resection after chemotherapy is usually required. A survival advantage has been demonstrated with neoadjuvant cisplatin-based chemotherapy, including chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), compared with no chemotherapy. Neoadjuvant chemotherapy is therefore considered the standard of care in muscle-invasive disease. More recently, accelerated or dose-dense MVAC regimens with growth factor support or gemcitabine–cisplatin regimens have been used in this setting. Carboplatin is less efficacious than cisplatin in urothelial carcinoma. Thus, even in patients who are ineligible for cisplatin-based therapy (usually due to decreased renal function, poor performance status, neuropathy, heart failure, or hearing loss), carboplatin-based regimens are not considered an adequate substitute, and such patients should instead be prioritized for cystectomy without neoadjuvant treatment or should be considered for a neoadjuvant clinical trial.

Adjuvant chemotherapy has generally been used to treat patients found to have pathologic T3 and T4 lesions or N+ disease after radical cystectomy. Several small, randomized trials have shown beneficial results for various adjuvant chemotherapy regimens; however large randomized multi-institution trials have failed to include a sufficient number of patients to demonstrate the superiority of adjuvant chemotherapy relative to chemotherapy administration at the time of relapse. The standard of care is to use neoadjuvant therapy in patients with muscle-invasive TCC. However, for patients who have not received neoadjuvant chemotherapy prior to cystectomy, it is reasonable to give cisplatin-based adjuvant chemotherapy to a subset of patients with pT3/T4 and/or pN+.

Chemotherapy in combination with radiation therapy has also been advocated as a bladder-preserving approach for muscle-invasive tumors. This approach is typically reserved for patients who are unfit for radical cystectomy or who have a strong desire to retain their bladder. Eligible patients undergo cystoscopy with maximal transurethral resection of bladder tumor (TURBT) and are then treated with concurrent chemotherapy and radiation therapy. Cisplatin is the appropriate concurrent agent if the patient has adequate renal function and is deemed eligible. For patients who are cisplatin-ineligible, treatment options include 5-fluorouracil with mitomycin C or gemcitabine. Following completion of chemoradiation, surveillance cystoscopies are performed. In the event of recurrence of muscle-invasive disease, a salvage radical cystectomy is typically performed as long as distant metastases are not also present. Concurrent chemoradiation appears to be particularly useful for smaller, lower-stage tumors. Approximately 30–50% of patients can attain long-term disease-free status with a functional bladder with this approach. Contraindications to this approach include the presence of **carcinoma in situ (CIS)**, multifocal tumors, and the presence of hydronephrosis or hydroureter, as these patients do less well with a bladder-sparing approach.

Metastatic Disease

The development of successful therapy of metastatic bladder cancer has been based on the use of cisplatin-based regimens. Historically, the combination of methotrexate, and vinblastine, doxorubicin (Adriamycin), and cisplatinum (MVAC) has been the most commonly used regimen. This regimen results in overall response rates of approximately 50–60% and complete remission rates in the 10–15% range. Median overall survival for patients with metastatic disease treated with this regimen is in the 12–14-month range. Despite early promise, however, long-term survival after MVAC remains low (only 10–15% alive at 5 years).

The combination of gemcitabine and cisplatin has been compared to MVAC and has been shown to be less toxic and roughly equivalent in efficacy to MVAC in patients with metastatic TCC. This regimen has largely replaced MVAC in the treatment of metastatic disease. It should be noted that the utility of the gemcitabine–cisplatin regimen as an adjuvant or neoadjuvant regimen has not been tested prospectively, although it has gained broad use in the neoadjuvant setting. For patients with metastatic disease with impaired renal function, agents such as carboplatin and paclitaxel have been utilized, although their efficacy is diminished relative to that of cisplatin-based regimens. The development of novel therapeutics for cisplatinum-ineligible patients is an important research priority.

Immunotherapy

Immunotherapy with checkpoint inhibitors has proven to be highly efficacious in a subset of patients with metastatic disease, where numerous agents have obtained FDA approval. The use of immunotherapy in earlier stages of bladder cancer as adjuvant or neoadjuvant therapy in muscle-invasive disease and in the treatment of non-muscle-invasive disease is also under investigation. These approaches are covered in Chapter 25.

RENAL CELL CARCINOMA

Metastatic Disease

The treatment of metastatic renal cell carcinoma (mRCC) with chemotherapy has proven to be largely unsatisfactory. With the development of novel targeted and immunotherapy agents over the past 10–15 years, essentially all practitioners have moved away from the use of chemotherapy in this malignancy. The RCC treatment landscape is rapidly evolving. Both chemotherapy and immunotherapy with interferon-α and high dose interleukin 2 have been replaced by small-molecule tyrosine kinase inhibitors (TKIs) targeting (in part) angiogenesis and the VEGF receptor. More recently, immunotherapy has had a renewed role with the development of checkpoint inhibitors that have improved clinical outcomes.

Selection of therapy for patients with metastatic or unresectable renal cell carcinoma is based on prognostic model risk grouping. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model is the most widely used. This model places patients into one of three risk categories based on six pretreatment variables: low hemoglobin (less than the upper limit of normal), high corrected calcium (greater than the upper limit of normal), elevated neutrophils (greater than the upper limit of normal), elevated platelets (greater than the upper limit of normal), time from diagnosis to start of treatment less than a 1 year, and Karnofsky performance status less than 80%. Patients are classified as having favorable risk if they have no risk factors, intermediate risk if they have one or two risk factors, and poor risk if they have three or more risk factors.

Appropriate front-line treatment options for patients in the favorable IMDC category include immunotherapy combination of ipilimumab and nivolumab or immunotherapy/TKI combination of pembrolizumab and axitinib.The use of single agent TKI in this setting with sunitinib or pazopanib is rapidly being replaced by these combinations. Front-line treatment options for patients with intermediate/poor IMDC risk include once again combination of ipilimumab with nivolumab or pembrolizumab and axitinib with an additional option of cabozantinib which can frequently be effective in patients with bone metastases. In the second-line setting, there are several options, depending on what front-line therapy has been used, including TKIs (axitinib, cabozantinib), immune therapy (nivolumab monotherapy), or the lenvatinib–everolimus combination—the combination of a TKI (lenvatinib) and an mTOR inhibitor, everolimus. These approaches are covered in Chapter 25).

Adjuvant Therapy

Numerous clinical trials have additionally assessed or are assessing the role of adjuvant treatment for high-risk disease following nephrectomy. Sunitinib has received FDA approval for the treatment of high-risk disease based on improvement in recurrence-free survival of about one year relative to placebo, but at the cost of significant toxicity. Furthermore, no overall survival benefit was observed in this trial. Trials of adjuvant immunotherapy regimens are underway.

PROSTATE CANCER

Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Two large international clinical trials (CHAARTED and STAMPEDE) demonstrated that the addition of docetaxel chemotherapy to standard-of-care ADT for patients with mHSPC significantly increased the overall survival in this patient population. In the CHAARTED trial the addition of six cycles of docetaxel (75 mg/m^2 every 3 weeks) provided an overall survival advantage of almost 14 months (57.6 months vs 44.0 months). Subset analyses revealed that this benefit was driven by patients with high-volume metastatic disease that was defined as having visceral metastases or having at least four bone lesions including at least one lesion outside the axial skeleton. No benefit was accrued to patients with less extensive disease. Approximately 6% of the patients who received docetaxel in this trial developed febrile neutropenia caused by docetaxel therapy. These data established the role of docetaxel in the treatment of patients with hormone-sensitive metastatic prostate cancer, particularly in the presence of high-volume metastatic disease. An oral androgen signaling inhibitor abiraterone was reported in two trials (LATITUDE and STAMPEDDE) to provide a magnitude of benefit that was virtually identical to that of docetaxel when given in combination with ADT in the same group of patients. An equally large survival advantage was seen. While LATITUDE treated only patients with extensive disease, the STAMPEDE trial has demonstrated benefit of abiraterone in lower volume patients. Updates of all these trials suggest that the hazard ratio may be more favorable for abiraterone, compared with docetaxel. In addition, abiraterone offers the option of a more favorable toxicity profile, the avoidance of chemotherapy, and the use of an oral agent, but requires long-term use compared with the relatively short (4.5-month) course with docetaxel.

▶ Castration-Resistant Prostate Cancer (CRPC)

A. Metastatic Disease

The systemic therapy of patients with metastatic prostate cancer in whom androgen deprivation therapy has failed generally consists of secondary hormonal manipulations followed by chemotherapy. Approximately 15% of patients who have had progressive disease despite therapy with combined androgen blockade will have a fall in PSA when their antiandrogen regimen is discontinued. This maneuver is mandated, therefore, before initiating other systemic therapy. In patients with mCRPC, both abiraterone and enzalutamide have substantial activity and are approved for use both before and after chemotherapy, although in practice, almost all patients are first treated with one of these agents prior to proceeding to chemotherapy. With regard to chemotherapy, the results of two phase III trials established docetaxel-based chemotherapy as the standard of care for first-line chemotherapy for mCRPC. Following therapy with docetaxel, patients who remain candidates for further chemotherapy can be treated with cabazitaxel, an agent shown to prolong life in this group of patients. Zoledronic acid or denosumab is indicated in castration-resistant prostate cancer (CRPC) patients with bone metastases, as each reduces the incidence of skeletal related events.

B. Nonmetastatic CRPC

In patients with nonmetastatic CRPC, two next-generation antiandrogens, apalutamide and enzalutamide, have been shown to delay the time to metastases by around 2 years, and are approved for use in this setting. The data from these studies suggest that earlier initiation of therapy targeting the androgen receptor is appropriate.

BIBLIOGRAPHY

ABCMC (Advanced Bladder Cancer Meta-analysis Collaboration): Neoadjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis. Lancet 2003;361(9373):1927–1934.

Bajorin DF, Bosl GJ: Bleomycin in germ cell tumor therapy: Not all regimens are created equal. J Clin Oncol 1997;15(5):1717–1719.

Beer TM, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. New Engl J Med 2014;371:424–433.

Beyer J et al: High-dose chemotherapy as salvage treatment in germ cell tumors: A multivariate analysis of prognostic factors. J Clin Oncol 1996;14:2638.

Beyer J et al: Long-term survival of patients with recurrent or refractory germ cell tumors after high dose chemotherapy. Cancer 1997;79:161.

Choueiri TK, et al: Cabozantinib versus everolimus in advanced renal-cell carcinoma. New Engl J Med 2015;373:1814–1823.

Choueiri TK, et al: Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle invasive urothelial cancer: Pathologic, radiologic, and biomarker correlates. J Clin Oncol 2014;32(18):1889–1894.

de Bono JS, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomized open-label trial. Lancet 2010;376:1147–1154.

Fizazi K, et al: Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomized, double-blind study. Lancet 2011;377:813.

Fizazi K, et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. New Engl J Med 2017;377:352.

Garrow GC, Johnson DH: Treatment of "good risk" metastatic testicular cancer. Semin Oncol 1992;19:159.

Grossman HB, et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. New Engl J Med 2003;349(9):859–866.

Hussain M, et al: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. New Engl J Med 2018;378(26):2465–2474.

IGCCCG (International Germ Cell Cancer Collaborative Group): International Germ Cell Consensus Classification: A prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15:594.

James ND, et al: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. New Engl J Med 2012;366:1477.

James ND et al: Addition of docetaxel, zolendronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. Lancet 2016;387:1163.

Kelly WK et al: Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. J Clin Oncol 1993;11:1566.

Motzer RJ, et al: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584–3590.

Motzer RJ, et al: Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer 2010;116:4256–4265.

Petrylak DP et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. New Engl J Med 2004;351:1513.

Plimack EJ, et al: Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: Results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol 2014;32(18):1895–1901.

Pont J et al: Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: Long-term results of a prospective trial. J Clin Oncol 1996;14:441.

Ravaud A, et al: Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. New Engl J Med 2016;375:2246–2254.

Rini BI, et al: Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomized phase 3 trial. Lancet 2011;378:1931–1939.

Ryan CJ, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. New Engl J Med 2013;368:138–148.

Savarese D et al: Phase II study of docetaxel, estramustine, and low-dose hydrocortisone in men with hormone refractory prostate cancer: A final report of CALGB 9780. J Clin Oncol 2002;19:2509.

Small EJ, Srinivas S: The antiandrogen withdrawal syndrome: Experience in a large cohort of unselected patients with advanced prostate cancer. Cancer 1995;76:1428.

Smith MR, et al: Apalutamide treatment and metastasis-free survival in prostate cancer. New Engl J Med 2018;378:1408–1418.

Sternberg SN et al: Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium: Efficacy and patterns of response and relapse. Cancer 1989;64:2448.

Sternberg CN, et al: Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): An intergroup, open-label, randomized phase 3 trial. Lancet Oncol 2015;16(1):76–86.

Sweeney CJ et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. New Engl J Med 2015;373:737.

Tannock I et al: Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: A Canadian randomized study with palliative end points. J Clin Oncol 1996;14:1756.

Tannock I et al: Docetaxel and prednisone or mitoxantrone and prednisone for advanced prostate cancer. New Engl J Med 2004;351:1502.

von der Maase H et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multi-national, multi-center phase III study. J Clin Oncol 2000; 17:3068.

Williams SD et al: Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathologic stage II testicular cancer. New Engl J Med 1987;317:1433.

Williams SD et al: Treatment of disseminated germ cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. New Engl J Med 1987;316:1435.

25

Immunotherapy in Urologic Malignancies

Arpita Desai, MD; & Eric J. Small, MD

Over the last decade an increased understanding of the complex interaction between immune surveillance and tumor growth has led to major advances in the field of immunotherapy. This has broadened application of immunotherapy in various malignancies. The goal of immunotherapy is to harness the body's immune system to recognize and target cancer. This chapter will highlight the basic principles of immunotherapy and describe the clinical application of immunotherapy in genitourinary malignancies.

PRINCIPLES OF CANCER IMMUNOLOGY

Innate and Adaptive Immunity

Innate and adaptive immunity are two facets of a healthy immune system required to mount an antitumor response. Innate immunity consists of natural barriers (skin, mucous membranes) along with defenses including neutrophils, natural killer cells, mast cells, dendritic cells, and macrophages. It is time-independent and usually the host's nonspecific first line of defense. In contrast, adaptive immunity includes T and B lymphocytes and is time-dependent, specialized, reactive to specific antigens, and capable of immunological memory. Dendritic cells, a type of antigen-presenting cell (APC), function as a link between the innate and adaptive immune systems. After acquiring and processing antigens, dendritic cells mature and present foreign antigens, generally derived from pathogens or tumor cells, to the T cells of the adaptive immune system. After the T and B cells are primed by the dendritic cells, they exert their antitumor response in an antigen-specific manner through cell-mediated immunity and production of antibodies, respectively. The interaction between the T-cell receptor (on the T cell) and major histocompatibility antigen complex (MHC) on the APC constitutes an immune synapse and is required for activation of T cells. The cytotoxic activity of T cells is regulated by numerous stimulatory and inhibitory receptors whose activity is closely regulated by cytokines. In particular, because uncontrolled immune activation can lead to the development of autoimmunity, there exist numerous normally occurring checkpoints designed to dampen an immune response. Thus, checkpoint receptors on T cells are upregulated by cytokines released with immune activation, bind to their ligands, subsequently inhibit T cell function, and thereby dampen and limit the immune response. Two highly relevant inhibitory (checkpoint) transmembrane protein receptors on lymphocytes are **cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)** and **programmed cell death 1 (PD-1)**. Both are expressed on lymphocytes (among other immune cells), upregulated by cytokines released following immune activation, and when bound to their ligand, downregulate immune responses. CTLA-4 activation and subsequent immune downregulation occur on binding B7-1 and B7-2 (CD80 and CD86) on the surface of APCs, while PD-1 binds to its ligand PD-L1, which is expressed on the surface of tumor cells and hematopoietic cells. The interaction between PD-1 and PD-L1 inhibits tumor lysis, enhances conversion of cytotoxic T cells to Treg cells, and causes peripheral T-cell exhaustion. These specific immune checkpoints are noteworthy because they have been successfully therapeutically targeted by checkpoint inhibitors, to eliminate this negative regulation, and allow an immune response to develop.

Immunoediting and Evading the Host Immune Response

Immunoediting refers to the dynamic process defining the relationship between cancer cells and the immune system. It is made up of three phases: elimination, equilibrium, and escape, and reflects the transition from successful immune surveillance to tumor growth.

1. **Elimination phase**: This phase is synonymous with immune surveillance and involves innate and adaptive host responses to cancer cells. It is characterized by activation of T cells, B cells, and NK cells by cytokines such as IFN-α, IFN-γ, and IL12, which are released from

tumor cells, macrophages, and surrounding stromal cells, and result in killing of tumor cells. Not all tumor cells are eliminated, and owing to the heterogeneity of tumors, fewer immunogenic tumors evade immune surveillance (equilibrium phase).

2. **Equilibrium phase**: This represents a balance between immune-mediated cancer killing and persistence of malignant clones. Tumor cells that have escaped the elimination phase usually have a nonimmunogenic phenotype and are preferentially selected for growth.
3. **Escape phase**: Tumor cells that escape from immune surveillance continue to grow rapidly, and malignant clones that have acquired the ability to escape the immune system emerge.

Cancers typically develop various mechanisms to evade the host immune response, including the following:

- Tumors promote an immunosuppressive microenvironment by increasing the secretion of certain cytokines such as IL6 and IL10 that result in infiltration of myeloid-derived suppressor cells (MDSCs) and regulatory T cells, both of which decrease the proliferation of cytotoxic lymphocytes.
- T-cell exhaustion by upregulation of immune checkpoints: PD-1 and PD ligand 1 (PD-L1)
- Overexpression of inhibitory indoleamine-2,3-dioxygenase (IDO), which promotes tumor growth
- Dysregulation of the antigen presenting process by which tumors could lose MHC expression

THERAPEUTIC AVENUES IN IMMUNE ONCOLOGY

A variety of therapeutic avenues are being pursued to activate the host immune system and control cancer. These approaches include cytokines, checkpoint inhibitors, vaccines, and T-cell engagement.

Cytokines

Cytokines are polypeptides that function as immunomodulating agents and play an essential role in cell signaling.

A. Interleukin 2

Interleukin 2 (IL2) has dose-dependent immunomodulatory and cytotoxic activity. High-dose IL2 causes expansion of CD8$^+$ T cells and NK cells, and facilitates differentiation of CD4$^+$ T cells to TH-1 and TH-2 cells exerting cytolytic activity on tumors. IL2 is FDA-approved for the treatment of metastatic clear cell renal cell carcinoma (RCC) (and malignant melanoma), where it results in an overall response proportion of 12–20%, a complete response rate of less than 10%, and produces long-lasting remissions in a very small subset of patients. The severe multiorgan toxicity associated with this regimen has limited its use to patients with normal organ function, high functional status, and relatively low tumor burden, and requires inpatient treatment at specialized centers capable of providing intensive medical care. The advent of checkpoint inhibitors (see discussion below), which are relatively well-tolerated, much more widely applicable, and administered in the outpatient setting, has largely eliminated the use of IL2.

B. Interferon Alfa

Interferon alfa 2b is a multifunctional immunoregulatory cytokine that activates the JAK-STAT pathway and transcribes interleukin 4, which is responsible for dedifferentiation of T helper cells to TH-2 helper cells, leading to stimulation of B cells and resulting in the production of antibodies. Used at one point for RCC, interferons have largely been replaced by immune check point inhibitors due to their superior therapeutic efficacy and safety.

C. Bacillus Calmette–Guerin (BCG)

The use of BCG intravesically for the treatment of superficial bladder tumors was first described in 1976. Over 40 years later, it continues to remain an important modality for treatment of non-muscle-invasive bladder cancer. Although the exact mechanism of action of BCG in bladder cancer is not completely understood, the robust local immune response is well recognized. The antitumor activity of BCG is thought to be mediated through several mechanisms, including induction of a local immune reaction mediated through activation of macrophages, dendritic cells, and NK cells through the activation of a myriad of cytokines. It also exerts a direct dose-dependent antitumor effect. Treatment with BCG has been proven to delay cancer progression, decrease the need for subsequent cystectomy, and improve overall survival.

Checkpoint Inhibitors

Checkpoint blockade removes inhibitory signals of T-cell activation, allowing T cells to mount an effective antitumor response. CTLA-4 is a transmembrane inhibitory protein expressed on lymphocytes. Immune dampening occurs when CTLA-4 binds B7-1 and B7-2 (CD80 and CD86) on the surface of APCs. Ipilimumab is an anti-CTLA-4 antibody that binds CTLA-4 and prevents it from binding B7-1 and B7-2. The elimination of this negative regulation allows an immune response to develop. Ipilimumab was the first immune checkpoint inhibitor to be approved because it prolonged survival in metastatic melanoma. It has since been studied in various malignancies and has been approved for use in various clinical settings, including advanced renal cell cancer. The clinical utility of CTLA-4 in urological malignancies is described in further detail below.

Similarly, the binding of the checkpoint inhibitory protein PD-1 on the surface of lymphocytes to its ligand PD-L1 on the surface of cancer cells results in immune inhibition. Several antibodies to PD-1 (pembrolizumab, nivolumab) and antibodies to PD-L1 (durvalumab, atezolizumab, avelumab) eliminate this negative regulation, result in improved survival, and are approved for use in melanoma, non-small-cell lung cancer, urothelial cancer, renal cell cancer, hepatocellular cancer, and gastric cancer. Details regarding the use of PD-1 inhibitors in genitourinary malignancies, both urothelial cancer and renal cell carcinoma, will be discussed later in this chapter.

Although the use of checkpoint inhibitors has transformed the care of advanced renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) patients, many questions remain. Checkpoint blockade induces durable responses across a wide range of tumors with a subset of patients achieving complete responses. These exceptional responses are unfortunately limited to a minority of patients, accentuating the need for novel therapeutic approaches. Furthermore, prostate cancer, the most common urologic malignancy, is largely unresponsive to checkpoint inhibition. Better understanding of the biological phenomena underlying effective immunological response has led to the use of various new therapeutic molecules in clinical trials. These include inhibitory molecules such as TIM3 and LAG3 and stimulatory molecules such as OX40 and 4-1BB, which are currently being studied in combination with PD-1 and CTLA-4 antibodies.

As a result of enhanced immune activity, a myriad of unique adverse events are associated with checkpoint inhibitors. Although these immune-related adverse events (IRAEs) can involve any organ system, they commonly involve the thyroid, skin, gastrointestinal system, liver, pancreas, lungs, and less frequently the cardiovascular and adrenal systems. It is important to note that IRAEs can mimic other conditions, resulting in misdiagnosis and improper management, underscoring the need for educating physicians on recognizing and managing these life-threatening adverse events.

Antibodies

Antibodies bind to proteins in their native form and have high specificity for antigens due to the presence of hypervariable regions within the antigen binding fragment or fab. Antibodies are modified to eliminate the foreign proteins by replacing them with human protein sequences, which significantly reduces their immunogenicity. Antibodies can be chimeric with mouse-antigen-binding domains or humanized with only hypervariable regions from the mouse. Antibodies can be modified and linked to other agents for targeting cancer cells. Examples include targeting radioisotopes, cytotoxic drugs, immune cytokines, and immune effector cells to the tumor.

Immunotherapy with monoclonal antibodies alone ("naked antibodies") has been extensively evaluated. The use of monoclonal antibodies against tumor-associated antigens has met with only limited success in patients with solid tumors, including prostate and kidney cancer. In lymphoproliferative disorders such as leukemia and lymphoma, some antibodies to tumor-associated surface antigens appear to result in tumor cell death. The mechanism for these effects is multifactorial but may, in part, be mediated by resultant complement fixation.

Direct antiproliferative effects of antibodies on cancer cells can be achieved by antibodies against functionally important antigens. Thus, the inhibition of growth factors and growth factor receptors and the activation or inhibition of signal-transducing molecules are attractive therapeutic targets. Kidney cancer is highly dependent on angiogenesis, and bevacizumab (an antibody against the proangiogenic molecule vascular endothelial growth factor [VEGF]) has been shown to prolong time to progression (TTP) in metastatic disease. Two independent randomized phase III trials have demonstrated the superiority of α-interferon plus bevacizumab over α-interferon alone, with an improvement in TTP, leading to approval by the US Food and Drug Administration (FDA) of bevacizumab for this indication. By contrast, in prostate cancer patients with progressive disease despite androgen deprivation therapy, the addition of bevacizumab to conventional chemotherapy with docetaxel failed to demonstrate a prolongation in the primary endpoint of the study, overall survival. Studies of bevacizumab in advanced bladder cancer have been undertaken; results are pending.

An alternative approach to naked antibodies is to conjugate any of a variety of cytotoxic agents to an antibody. The advantage of this approach is a "bystander effect," making it unnecessary to use an antibody that binds each cell. This can be achieved in a variety of ways. The most straightforward is to use the monoclonal antibody as a means of providing some targeting specificity for the cytotoxic agent used. Cytotoxic agents used include radioisotopes, chemotherapy, and toxins. Examples of this approach are the coupling of the radioisotope lutetium-177 to an anti-PSMA antibody or small molecule, which is under investigation in prostate cancer.

Vaccines

Autologous vaccination programs (the vaccination of patients with their own tumor cells) have been extensively explored. The advantage of autologous vaccination is that the vaccine bears the antigens of the patient's tumor, although the distinct disadvantage is that not every patient has a tumor available for vaccine preparation, and the preparation of each vaccine is tremendously labor-intensive. By contrast, allogeneic vaccines (the use of a generic vaccine or "off the shelf" antigen) have the benefit of mass production and ease of use, and the identification of specific tumor rejection antigens allows specific antigenic targeting. However, this approach runs the risk of a narrower shared antigenic spectrum with the patient's tumor. Both autologous and allogeneic vaccination strategies have been evaluated in RCC and prostate cancer.

Several means exist to undertake vaccination. The simplest is to use intact but inactivated tumor cells. Inactivation can be achieved with ultraviolet radiation, external-beam (photon) radiation, or freeze–thawing. Crude extracts of cells can also be used. The advantage of using cell extracts is that inactivation is not necessary and small particles and proteins that might be more easily phagocytosed are available. One can also enhance the immunogenicity of inoculated cells by growing the cells in cytokines, coinjecting with cytokines (nonspecific active immunotherapy, described later), or transfecting these cells with the genes for immune stimulatory cytokines or the costimulatory molecule B7. Clinical trials using prostate cancer cell lines transfected with the granulocyte–macrophage colony-stimulating factor (GM-CSF) gene for vaccination in patients with metastatic hormone refractory prostate cancer failed to show a therapeutic benefit. Purified protein or peptides represent a second potential vaccination schema. Early trials of PSA in a vaccinia and fowlpox (ProstaVax) vector demonstrated clinical activity, but a large phase III trial did not demonstrate an overall survival benefit. A third way of undertaking specific vaccination is to attempt to bypass the antigen-presenting function of the immune system and to directly stimulate professional antigen-presenting cells, such as dendritic cells, ex vivo. These cells can be stimulated by pulsing them with protein or peptides of interest or by transfecting them with a gene encoding the antigenic peptide of interest before reinfusion. Sipuleucel-T is an autologous dendritic cell, in which a cellular product enriched for APCs is pulsed with prostatic acid phosphatase. Sipuleucel T has been shown to prolong life in men with mCRPC and is appropriate for patients who do not have cancer-associated pain, visceral metastases, rapidly progressive disease, or the need for systemic steroids.

T-Cell Engagement

Adoptive T cell broadly involves the practice of isolation and ex vivo expansion of tumor-specific T cells to achieve greater specificity. There are various forms for T-cell engagement in use; chimeric antigen receptors (CAR-T) and bispecific T-cell engagement are discussed below. There are currently no T-cell-engaging therapies approved for use in any solid tumor, including urologic malignancies, but their potential warrants mentioning them.

A. Chimeric Antigen Receptors

The development of chimeric antigen receptor (CAR) T cells provides the combined advantages of enhanced specificity, amplified response, and immunological memory.

Ex vivo modification of T cells to express CAR, which combines both the antigen-binding domain from a B-cell receptor (in which the target antigen can be selected) to the intracellular signaling domain of CD3 T-cell receptor (to bind and activate T cells) into a single chimeric protein, is referred to as **CAR-T cell therapy**. These artificially programmed T cells are able to target specific antigens present on the surface of tumor cells independently of MHC recognition. CAR T cells can be derived autologously (from the patient's own blood) or allogeneic (derived from a donor's T cells). Harvested T cells are genetically engineered ex vivo to express a specific chimeric antigen receptor, targeting a tumor antigen. The selected tumor antigen is generally not expressed on benign tissues to limit toxicity. Once infused back into the patient, these CAR-T cells acting as "living drugs" are activated on contact with the prespecified tumor antigen and result in destruction of the tumor through the production of a variety of cytokines and interleukins. CAR-T cells have shown remarkable efficacy in certain hematologic malignancies and became available for commercial use in 2017. Durable complete responses were observed for over 3 years have been observed in some patients. The common toxicities were due to cytokine release syndrome and tumor lysis syndrome.

B. Bispecific T-Cell Engagement

Blinatumomab is a bispecific T-cell engager (BiTE) that has dual specificity for CD19 expressed on malignant B cells and CD3 on T cells. Tumor lysis is mediated through the production of inflammatory cytokines, proliferation of T cells resulting in the lysis of CD19 cells. Blinatumomab was approved by the FDA for relapsed or refractory precursor B cell lymphoblastic leukemia (B-ALL). Ongoing trials are using BiTE technology to target PSMA + cells in patients with advanced prostate cancer.

APPROVED IMMUNOTHERAPY IN GENITOURINARY MALIGNANCIES

Prostate Cancer

A. Vaccines

Sipuleucel-T is an autologous dendritic cell therapeutic vaccine that enhances immune T-cell response to prostate acid phosphatase (PAP) and serves as individualized immunotherapy for men with advanced castrate-resistant prostate cancer with asymptomatic or minimally symptomatic castrate resistant prostate cancer. The vaccine is prepared by harvesting peripheral blood mononuclear cells obtained by leukapheresis, which are then exposed ex vivo to a recombinant protein consisting of PAP fused to human granulocyte–macrophage colony-stimulating factor (GMP-CSF). Sipuleucel-T is administered for a total of three treatments at 2-week intervals. In two phase III randomized studies, sipuleucel-T prolonged survival compared with placebo vaccine and led to the approval of this agent. It is important to note that patients with visceral metastasis and with significant cancer-associated pain requiring opioid analgesics were excluded from these trials.

Several phase I and II trials demonstrated objective PSA responses with ProstaVax, which is a vaccinia–fowlpox virus that was genetically modified to express human PSA gene along with a series of immune adjuvants to enhance its immune response. However, a large phase III study failed to confirm these responses with no significant difference in overall survival.

B. Checkpoint Inhibitors

In men with castrate-resistant prostate cancer, checkpoint inhibition with anti-CTLA-4 (ipilimumab) was evaluated in two phase III studies and failed to show a survival benefit. Thus far, checkpoint inhibition with anti-PD1 or anti-PD-L1 antibodies has also failed to demonstrate significant activity in mCRPC, with one notable exception in a very small subset of patients.

DNA mismatch repair is a system of correcting errors that occur during the process of DNA replication, recombination, and during DNA repair. Tumors with defective DNA mismatch repair (dMMR) have additional mutations leading to increased neoantigens that are recognized as non-self-antigens. These tumors have high microsatellite instability (MSI-H), account for approximately 2–3% of patients with advanced prostate cancer, and are sensitive to PD-L1 inhibitors. Pembrolizumab was granted accelerated approval by the FDA for treatment of patients (of any solid tumor type) with unresectable or metastatic progressive MSI-H or dMMR cancer. Therefore, in the mCRPC setting, it is essential to evaluate tumors by next-generation sequencing for MSI status, to identify patients who could benefit from immunotherapy.

Urothelial Cancer

A. Localized Bladder Cancer

About 70% of urothelial malignancies are classified as non-muscle-invasive (NMI) at initial diagnosis. The primary treatment commonly involves transurethral resection of visible bladder tumor (TURBT). Recurrence is commonly seen with TURBT alone and is estimated to be around 40–80% within 6–12 months from TURBT. Thus, additional therapy is warranted after TURBT. Bacillus Calmette–Guérin (BCG) is a live attenuated form of tubercle bacillus that appears to have local activity against some tumors but has been largely disappointing as systemic therapy. The mechanism by which BCG can elicit a local immune response in the uroepithelium and thereby exhibit impressive anticancer activity is not well delineated. However, possible mechanisms of action include macrophage activation, lymphocyte activation, recruitment of dendritic cells, and natural killer cells. As discussed in Chapter 24, BCG is highly effective in NMI bladder cancer. It is intriguing that this is strictly a local phenomenon and that BCG has no role in the treatment of muscle-invasive or metastatic disease.

Immunotherapy with checkpoint inhibitors is being investigated in the early stages of bladder cancer as adjuvant or neoadjuvant therapy in both muscle-invasive and non-muscle-invasive disease, but to date, no definitive data have been reported.

B. Metastatic Urothelial Cancer

Cisplatin-based chemotherapy is the backbone of therapy in patients with metastatic urothelial cancer. This has been described in further detail in Chapter 24. However, a large proportion of patients are not eligible to receive a platinum-based regimen, due to concomitant comorbidities such as impaired renal function, neuropathy, and heart failure. Immunotherapy with checkpoint inhibitors has proven to be highly efficacious in a subset of patients with metastatic disease, where a number of agents have obtained FDA approval. Both pembrolizumab and atezolizumab have been shown to have significant activity superior to non-platinum-based chemotherapy in the front-line setting in patients who are platinum-insensitive, leading to their FDA approval for this indication.

Checkpoint inhibitors have also been evaluated in patients who have progressed after front-line platinum-based therapy. Five remarkable antibodies (atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab) have been approved by the FDA for patients who have progressed during or after platinum-based chemotherapy. There is no immediately apparent reason to choose one of these agents over another, although direct comparisons have not been undertaken.

The use of checkpoint inhibitors both as front-line therapy for metastatic disease, and in earlier stages of bladder cancer as adjuvant or neoadjuvant therapy in muscle-invasive disease and in the treatment of non-muscle-invasive disease is also under investigation.

Renal Cancer

Renal cell cancer is a highly immunogenic tumor and has long been a “poster child” for the use of immunotherapy. Historically, cytokine-based therapies (IFN-α and IL2) were used as first-line therapy for advanced RCC and were associated with durable responses and improved survival in a small subset of patients. Unfortunately, the severe associated toxicity and inability to select patients who could potentially respond have precluded their widespread use. Over the past decade, a number of multiple-kinase tyrosine kinase inhibitors targeting vascular endothelial growth factor receptors (VEGFRs) and mammalian target of rapamycin (mTOR) have been standard of care for patients with advanced RCC. TKIs have been explained in further detail in Chapter 19. Although these resulted in prolonged progression-free survival and improved response rates, they invariably result in treatment resistance and thus do not provide durable long-term responses.

Treatment recommendations in advanced and unresectable renal cell cancer is based on the extent of disease, histologic subtype, and the commonly used International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model, which classifies patients into three prognostic risk groups based on six pretreatment variables (performance status, low hemoglobin, elevated neutrophil count, elevated platelet count, elevated calcium, and diagnosis to treatment initiation < 1 year).

Immunotherapy has changed the treatment landscape in renal cell cancer. A phase III study demonstrated an improvement in overall survival, progression-free survival, and overall response rates in patients with intermediate and poor IMDC risk who received combination ipilimumab–nivolumab immunotherapy compared to the standard of sunitinib alone. Patients with PD-L1 expression (>1%) had superior responses on the immunotherapy combination arm compared to the low-PD-L1 expressers. Consequently, ipilimumab and nivolumab were approved by the FDA for the treatment of naive intermediate- and poor-risk advanced RCC. A checkpoint inhibitor, nivolumab with or without ipilimumab, is commonly used in the second- and additional-line setting in advanced clear-cell RCC who have progressed on prior TKI therapy.

Further understanding of the interaction between angiogenesis and immune modulation has led to the development of clinical trials combining TKIs with checkpoint inhibitors. Angiogenesis blocking by VEGF inhibition has been shown to increase T-cell infiltration in tumors and enhance immune response by increased expression of PD-1 and PD-L1 expression. Recently, two phase III studies showed superior outcomes combining the TKI axitinib with one of two checkpoint inhibitors, either pembrolizumab or avelumab. Benefit was seen across all subgroups. To date, the FDA has approved the pembrolizumab–axitinib combination (on April 22, 2019) and Avelumab-axitinib combination (on May 14, 2019) for the front-line treatment of patients with advanced RCC based on data from a phase III trial demonstrating significantly improved, progression-free survival, and overall response rates with the combination compared to sunitinib. It is important to note that pembrolizumab plus axitinib resulted in improvement in overall survival where as there is no overall survival benefit reported with avelumab in combination with axitinib. Several other trials combining other checkpoint inhibitors with TKIs are in progress. With immunotherapy and TKI combination trials reporting enhanced efficacy, the optimal sequence of therapies for patients experiencing progressive disease on these combination studies remains an important clinical issue.

BIBLIOGRAPHY

Anonymous: FDA approves pembrolizumab plus axitinib for first-line treatment of advanced renal cell carcinoma. 2019. (Available online at: https://ascopost.com/News/59965; accessed 4/22/19.) FDA Approves Avelumab/Axitinib Combination for Advanced Renal Cell Carcinoma (Available online at https://ascopost.com/News/60049)

Atkins MB, et al: High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17(7):2105–2116.

Eder JP, et al: (2000). A phase I trial of a recombinant vaccinia virus expressing prostate-specific antigen in advanced prostate cancer. Clin Cancer Res 2000;6(5):1632–1638.

Fesnak AD, June CH, Levine BL: Engineered T cells: The promise and challenges of cancer immunotherapy. Nat Rev Cancer 2016;16(9):566–581.

Fuge O, Vasdev N, Allchorne P, Green JS: (2015). Immunotherapy for bladder cancer. Res Rep Urol 2015;7:65–79.

George S, Rini BI, Hammers HJ: (2018). Emerging role of combination immunotherapy in the first-line treatment of advanced renal cell carcinoma: A review. JAMA Oncol 2018.

Gulley JL, et al: Phase III trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. J Clin Oncol 2019:JCO1802031.

Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell 2011;144(5):646–674.

Jacobson CA, Ritz J: Time to put the CAR-T before the horse. Blood 2011;118(18):4761–4762.

June CH, Riddell SR, Schumacher TN: Adoptive cellular therapy: A race to the finish line. Sci Transl Med 2015;7:280–287.

Kantarjian H, et al: (2017). Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376(9):836–847.

Le DT, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357(6349):409–413.

Liu XD et al: Resistance to antiangiogenic therapy is associated with an immunosuppressive tumor microenvironment in metastatic renal cell carcinoma. Cancer Immunol Res 2015; 3(9):1017–1029.

Makkouk A, Weiner GJ: (2015). Cancer immunotherapy and breaking immune tolerance: New approaches to an old challenge. Cancer Res 2015;75(1):5–10.

Mellman I, Coukos G, Dranoff G: (2011). Cancer immunotherapy comes of age. Nature 2011;480(7378):480–489.

Motzer RJ et al: Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New Engl J Med 2019;380(12):1103–1115.

Motzer RJ et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New Engl J Med 2007;356(2):115–124.

Postow MA, Callahan MK, Wolchok JD: (2015). Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33(17):1974–1982.

Rini BL et al: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New Engl J Med 2019;380(12): 1116–1127.

Rosenberg JE, et al: Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet 2016;387(10031):1909–1920.

Schreiber RD, Old LJ, Smyth MJ: (2011). Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science 331(6024):1565–1570.

Small EJ, et al: Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006;24(19):3089–3094.

Wei SC, Duffy CR, Allison JP: (2018). Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 2018;8(9):1069–1086.

Radiotherapy of Urologic Tumors

26

Yun Rose Li, MD, PhD; Alexander R. Gottschalk, MD, PhD; &
Mack Roach III, MD

Radiation has played an important role in the primary management of genitourologic malignancies for more than 100 years. In 1895, Wilhelm Roentgen described x-rays; by 1899, a patient with skin cancer was cured with radiation; and within 10 years, radiation was used to treat prostate cancer. Radiotherapy has become a mainstay of treatment for cancers arising from the bladder and testes and prostate and to a lesser degree of penile, urethral, and kidney cancers as megavoltage sources became available, despite advances in chemotherapy and aggressive surgery. Moreover, the advent of dose-escalated, short-course radiation therapy such as stereotactic body radiation (SBRT), has opened new avenues for the use of radiation in the treatment of genitourinary malignancies (Gonzalez-Motta and Roach, 2017; Kishan et al, 2019a; Morgan et al, 2018). In this chapter, we review general principles and the indications for using radiation as a component in the primary management of urologic malignant diseases. Although radiation also plays a major role as an agent of palliation, this information has been well documented elsewhere and is excluded from this chapter (Hansen and Roach, 2018; Bourgeois 3rd et al, 2011; Carl et al, 2019).

GENERAL PRINCIPLES OF RADIOTHERAPY

Mechanisms of Cytotoxicity

The effects of radiation on tumor and surrounding normal tissues are thought to be mediated primarily through the induction of unrepaired double-strand breaks in DNA (McMahon and Prise, 2019; Tang et al, 2019). This can be attributed to the direct impact to the DNA strand but more frequently may be due to the secondary effect of excited electron species generated in the presence of oxygen from peroxide radicals. These unstable scavenger molecules then interact with nucleotide bases, and the consequent damage to the DNA may lead to the generation of either repairable or nonrepairable DNA double-strand breaks during mitotic division. High-linear-energy-transfer radiation (including neutrons, protons, carbon, and other heavy-charge particles) is associated with greater biological effect because of its ability to induce direct, physical double-strand breaks. However, as the vast majority of DNA in a cell is not being actively transcribed, the cytotoxic impact of radiation may not be observed until the radiated cells enter mitosis. Postmitotic normal tissues with low mitotic activity, such as the heart, brain, and spinal cord, tend to express the effects of radiation much later than do cells from actively dividing tissues, such as the epithelial cells lining the rectum, bladder, or urethra. This process leads to apoptosis of cells with irreparable DNA damage and enables tissue regeneration by mitosis. However, cells in postmitotic normal tissues with low mitotic activity are more sensitive to the use of high-dose-per-fraction or high-linear-energy-transfer radiotherapy because fewer cells turn over, and therefore accumulated DNA damage may not result in cell death and elimination of cells that then would have abnormal genetic material (Allen et al, 2015). In organs in which the functional stromal cells are postmitotic, such as muscle cells and neurons, the damage is expressed by slowly dividing support cells such as endothelial cells. Although results from animal models suggest that it is better to achieve androgen suppression before starting radiation treatment, in humans this may be sequence- and volume-dependent as well and may not mirror the effects seen in animal models (Zietman et al, 2010; Roach et al, 2018).

Radiation Sensitivity and Tolerance

Radiation tumor responses and the tolerance of normal tissues are dependent on the biological effective dose given and the characteristics of a given tissue. The most common patterns of practice involve the use of definitive external-beam radiation delivered using **conventional fractionation**, traditionally given as single daily doses ranging from 180 cGy (1.8 Gy) to 200 cGy (2.0 Gy). When used as the primary treatment, cumulative doses of 70–81 Gy are typical for local control of gross disease (adenocarcinomas, transitional cell carcinomas [TCCs], and squamous cell carcinomas) arising from the prostate, bladder, urethra, or ureters. When used **prophylactically** for presumed microscopic residual local disease or in lymph nodes postoperatively, doses of 45–70 Gy are typical. For testicular seminomas, doses of as low as 25 Gy may be adequate in the definitive setting.

The total dose delivered and the dose per fraction are associated with the risk of acute (during or within the first <3–6 months of treatment) and late radiation-induced complications. Several additional factors appear to increase the risk of radiation-induced complications, including previous radiation, surgery, concurrent systemic therapy, smoking, diabetes, some genetic (Li-Fraumeni), autoimmune, or collagen vascular disorders (eg, inflammatory bowel disease, lupus, scleroderma), older age, and other genetic factors, only recently recognized (Ahmed et al, 2016; Kerns et al, 2010; Andreassen et al, 2016; Azria et al, 2017; Kerns et al, 2016; Oh et al, 2017). Accurate estimates of the "true tolerance" of surrounding normal tissues have been limited until recently by our inability to reconstruct the actual relationship between normal tissue doses and volumes in three dimensions. Early reports assumed that organ movement and day-to-day treatment setup error had an insignificant impact on the doses of radiation delivered to surrounding normal tissues. Studies have demonstrated that these assumptions are inaccurate and probably result in an underestimate of the true tolerance of surrounding normal tissues to radiation (Langen and Jones, 2001).

Dose per Fraction Considerations

The linear quadratic equation (LQ equation) has been adopted by many clinical investigators as the most useful model for comparing the relatively biological effect of different dosing and fractionation schemes (Fowler et al, 2001) This equation can be written as follows:

$$\text{Effect (E)} = n\,(\alpha d + \beta d)$$

where

d = dose per fraction

α = nonrepairable effects

β = repairable effects

n = number of identical fractions

For comparison of two different fractionation schemes, assuming a similar overall treatment time, the LQ equation also can be written as follows:

$$D_2/D_1 = (1 + d_1\beta/\alpha)/(1 + d_2\beta/\alpha)$$

where

D = total dose and $D_1 = n_1 d_1$

d = dose per fraction

For most clinical circumstances, it is assumed that the α/β ratio for late-reacting normal tissues such as the bladder or rectum is 3. For early-responding normal tissues and for tumor, it is assumed that the α/β ratio is 10.

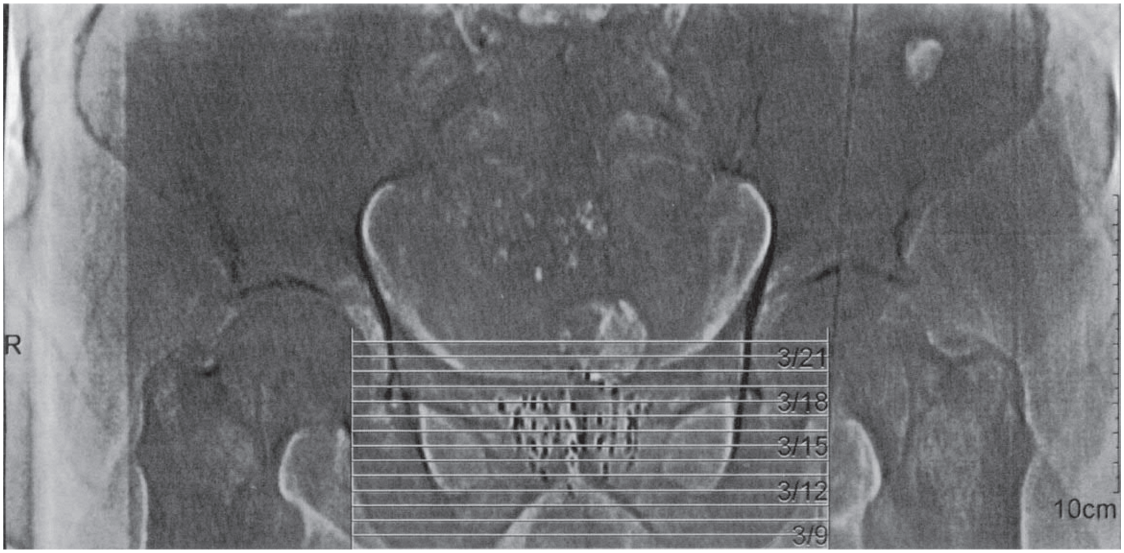
Altered Fractionation Schedules

Classically, radiobiologic modeling incorporates a concept for estimating biologic effects based on the so-called α/β ratio. Calculations using this α/β ratio are generally supported by clinical outcome data demonstrating that there are biological advantages to the use of large versus small fractions, as well as reduced cost and patient convenience. The notion that the use of "altered fractionation schedules" may improve the therapeutic ratio between efficacy and toxicity; in other words, improving the biological effective dose to the tumor without increasing normal tissue toxicity is accepted by most but not all authorities (Dearnaley et al, 2016; Johnson et al, 2016; Incrocci et al, 2016).

Hypofractionation involves the use of larger than "conventional" fraction sizes and fewer total fractions. Such an approach could result in a reduction in the total biologic doses to normal tissues (potentially reducing late complications) without compromising efficacy, if the α/β ratio for tumor is low relative to surrounding the normal tissues (Fowler et al, 2001). A number of investigators have argued that the α/β ratio for prostate cancer is quite low, providing a strong rationale for the use of hypofractionation and ultrahypofractionation as is done with high-dose-rate (HDR) brachytherapy and/or stereotactic body radiotherapy (SBRT) (Brenner and Hall, 1999; Fowler et al, 2001; King and Fowler, 2001). Hypofractionated radiotherapy most certainly shortens overall time and cost, but to date, only one randomized trial suggests that cancer control rates might be better (Arcangeli et al, 2010; Lee, 2009; McCammon et al, 2009; Ritter et al, 2009). Although some studies suggest that there is no therapeutic advantage, others support the notion that there may be advantages and that evidence-based guidelines are generally more supportive for hypofractionation than for ultrahypofractionation schedules (Morgan et al, 2019; Kishan, 2019a). Because of day-to-day setup variation, some type of online monitoring is advisable, to ensure that treatments can be carried out as accurately and safely as possible, particularly with ultrahypofractionation (eg, SBRT regimens) (Alejandro Gonzalez-Motta and Roach 2017).

Brachytherapy

The term **brachytherapy** refers to a treatment technique that places radioactive sources in close proximity to or directly into the tumor. Brachytherapy can be classified as either (1) interstitial or intracavity and (2) permanent or low dose rate (LDR) or temporary or high dose rate (HDR) (Bermudez et al, 2007; Viswanathan et al, 2011). Interstitial brachytherapy involves the placement of radioactive needles, afterloaded needles or catheters, or radioactive seeds directly into the prostate, bladder, penis, or periurethral soft tissues. Intracavitary brachytherapy includes placement of radioactive



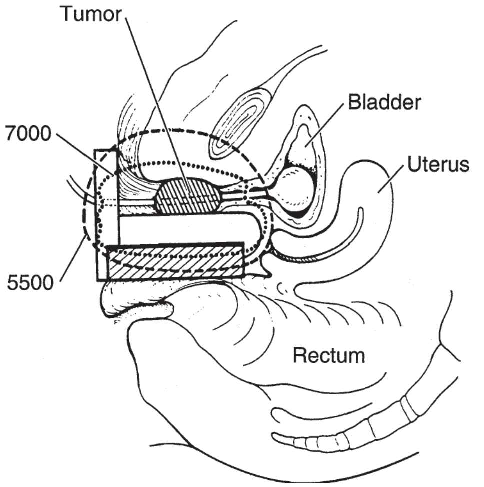
▲ **Figure 26–1.** Brachytherapy: example of an ultrasound-guided permanent interstitial implant of the prostate.

catheters into a lumen or orifice, such as in the urethra, to treat urethral and penile tumors. Permanent implants involve the use of radioactive seeds that are left in the patient. Modern temporary implants generally involve the use of needles or catheters that act as conduits for delivering radiation through high-activity seeds that are attached to a long wire, and all radioactive materials are removed at the end of the procedure. Most modern temporary implants delivered using HDR brachytherapy systems deliver moderately high doses of radiation over a relatively short period of time (minutes). HDR brachytherapy can be delivered as a single session but more often as two or more treatment sessions to reduce the risk of late complications and possibly reduced efficacy (Canadian trial showing 2 > 1 F*x*). Low-dose-rate (LDR) brachytherapy is usually delivered in a continuous fashion over months via placement of permanent radioactive seeds that treat the tumor as the radioactive source activity decays over time (Sahgal and Roach 2007). Figure 26–1 depicts an example of a transrectal ultrasound–based iodine-125 permanent interstitial implant of the prostate. Figure 26–2 shows an example of intracavitary brachytherapy for a urethral tumor in a female patient.

SPECIFIC UROLOGIC SITES

Prostate Cancer

Few urologists are aware that radiotherapy was first used to successfully treat prostate cancer more than 100 years ago and that it was not until 1949 that Memmelaar first reported the successful use of the radical retropubic prostatectomy (RRP) for treatment of prostate cancer (Memmelaar 1949). In the 1950s and 1960s, it was believed that radiotherapy, as compared to prostatectomy, provided comparable results with less morbidity. However, in 1979, Walsh and Donker demonstrated the potential value of the RRP to preserve nerves (Elder et al, 1982), and later, Walsh and others reported improvements in the RRP that promised to reduce blood loss, minimize the risk of incontinence, and preserve potency (Reiner Walsh 1979). The comparative effectiveness of RRP

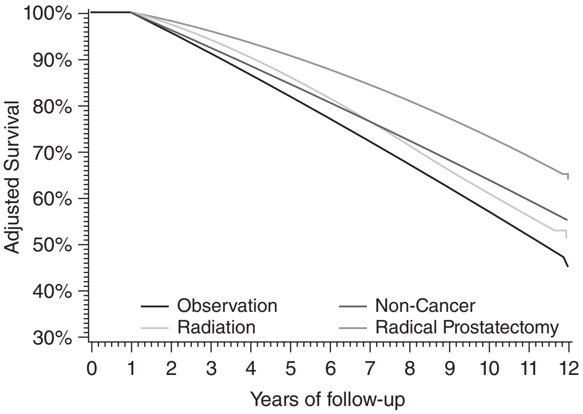


▲ **Figure 26–2.** **Example of intraluminal brachytherapy for urethral cancer.** (Reproduced with permission from Sailer SL, Shipley WU, Wang CC: Carcinoma of the female urethra: A review of results with radiation therapy. J Urol. 1988 Jul;140(1):1–5.)

versus treatment with radiotherapy is very controversial in part because of the potential for selection bias, as more favorable patients and younger patients with fewer comorbidities tend to undergo surgery.

For example, Giordano and colleagues attempted to systematically evaluate the effect of selection biases in observational studies of treatment effectiveness in men with localized prostate cancer (Giordano et al, 2008). They identified men from the Medicare-linked database—surveillance, epidemiology, and end results. They noted that controlling for comorbidity, extent of disease, and other characteristics by multivariate analyses or by propensity analyses had remarkably small impact on these improbable results. They concluded that observational studies of treatment outcomes should be viewed with caution. As is shown in Figure 26–3, they noted that men treated by radical prostatectomy had a better adjusted survival rate than men without prostate cancer, suggesting selection biases for favorable outcomes for these men compared with those treated with radiotherapy.

An additional challenge to comparing outcome between RP and RT is the fact that there have been major advances in technologies impacting the accuracy of radiation delivery, making this treatment somewhat of a "moving target." These relatively rapid advances in technology enabling dose escalation and treatment precision, and the incorporation of hormonal therapy, made it very challenging to include them in comparative studies, while addressing selection bias. Thus, while some retrospective studies suggest better outcomes with surgery, inherent biases shed doubt on the validity of these conclusions (Roach et al, 2015; Wallis et al, 2015, 2016). The complexity of treatment choices in the management of prostate cancer makes treatment decision making particularly challenging. The specific considerations and recommendations used at our institution are summarized in Table 26–1.



▲ **Figure 26–3.** **As is shown, men treated by radical prostatectomy had a better adjusted survival rate than did men without prostate cancer, suggesting selection biases for favorable outcomes for these men compared with those treated with radiotherapy.** (Reproduced with permission from Giordano SH, Kuo YF, Duan Z: Limits of observational data in determining outcomes from cancer therapy, Cancer. 2008 Jun;112(11):2456–2466.)

Prostate-specific antigen (PSA) control rates appear to be very similar between contemporary high-dose radiation and surgical series (Jabbari et al, 2010; Kupelian et al, 2004; Stone et al, 2009; Grimm et al, 2012). The few prospective phase III randomized trials completed recently comparing RT against RRP have failed to report significant differences in oncologic outcomes, although differences in rates of short- and long-term toxicity were noted (Hamdy et al, 2016; Lennernas et al, 2015).

Many patients whose disease was once thought to be controlled locally, based on physical examination, do in fact have persistent disease when assessed by PSA or biopsy, or both (Crook et al, 2000). Although the posttreatment PSA is more sensitive, it is a less specific endpoint for treatment failure than is biopsy, because regional and distant failures can contribute to a rising level. PSA has been long recognized as an acceptable endpoint for the assessment of disease status, but over the last few years, its value and limitations after radiotherapy has become clearer (Roach et al, 2003, 2006a, 2007; Rodrigues et al. 2011; Morris et al. 2014; Michalski et al, 2012). The most commonly accepted definition for a recurrence after radiation is the "Phoenix definition," which is met when a patient's PSA rises by more than 2 ng/mL above the nadir (lowest) postradiation value (Roach et al, 2006b). It should be noted that the threshold for postradiation recurrence thus differs from the threshold for recurrence after prostatectomy. Unfortunately, although the posttreatment PSA is the most sensitive way to monitor for biochemical recurrence, pretreatment PSA is not the most important predictor of survival.

The pretreatment PSA appears to be less important than the Gleason score (GS) or the T stage (Roach et al, 2007; Rodrigues et al, 2011). The importance of the GS and T stage has been well demonstrated by the long-term results of phase III randomized trials conducted by the Radiation Therapy Oncology Group (RTOG) (Roach et al, 2000). In a multivariate analysis, the Gleason score, the clinical stage, and pathologic node status were correlated with overall and cause-specific survival. The use of this type of risk stratification system to predict overall survival has been validated using contemporary patients (Roach et al, 2007). A benefit of the RTOG risk groups is their use in defining for whom and how long hormonal therapy should be used. Numerous other risk stratification schemes are currently in popular use by radiation oncologists in the management of prostate cancer, but the greatest degree of consensus is probably the groupings recommended by the National Comprehensive Cancer Network (NCCN) (Carroll and Mohler, 2018).

Recent studies have raised questions as to whether better risk stratification could be achieved using histologic subtyping and/or genomic classifiers to determine the benefits of and guide the use of ADT (Dalela et al, 2017; Ross et al, 2014; Zhao et al, 2017).

Table 26–1. Radiation therapy "preferred" options and relative contraindications for prostate cancer at UCSF (2017).[a]

Type of radiotherapy	Year[a]	Primary indications	Relative contraindications
IGRT (image guided radiotherapy)[b]	Pre-1996	Combination therapy pre/postboost treatment Postop adjuvant treatment Postop salvage treatment Large TURP defects Other options not covered by insurance Patient preference	Previous full-dose radiation Patient preference (eg, logistically problematic) Focal recurrence (favor focal treatments) Technical issues (eg, too large for CT scan but BT-suitable) Inflammatory bowel disease or connective-tissue disorder Noncompliant for many visits
PPI (permanent prostate implant) BT (brachytherapy)	1996	Monotherapy for low- or favorable intermediate-risk patients Boost in clinical T1–T2 with IMRT Focal salvage postrecurrence after IMRT Focal salvage postrecurrence after PPI Patient preference	Not a candidate for anesthesia Discontinuation of anticoagulation is unadvisable Excessive pubic arch interference (PAI) Excessively large TURP defect Severe baseline urinary symptoms (eg, urinary retention)
HDR (high-dose-rate) BT	1999	Monotherapy for low- or favorable intermediate-risk patients Boost in clinical T1–T3 with IMRT Focal salvage postrecurrence after IMRT Pubic arch interference prohibiting PPI Median lobe too large for SBRT Insurance prohibits SBRT Patient preference	Not a candidate for anesthesia Discontinuation of anticoagulation is unadvisable Excessive pubic arch interference Excessively large TURP defect Severe baseline urinary symptoms (e.g. urinary retention)
SBRT (stereotactic body radiation therapy)	2005	Monotherapy for low- or favorable intermediate-risk patients Boost for clinical T1–T4 with IMRT Focal salvage in selected patients postrecurrence after IMRT when not candidate for BT salvage Patients presenting with obstruction due to locally advanced disease (eg, "reverse" boost) Patient preference (eg, convenience)	Very large median lobe Unable to lie still and flat for 45 minutes (eg, tremor) Poor localization due to metal artifacts (eg, hip replacement, presence of PPI seeds) Poor seed positioning ("too close") Not covered by insurance Protocol requires other treatments

[a] Approximate year program started at UCSF.

[b] Delivered with either conventional or hypofractionation. The term "primary preferred" reflects the clinical nuances that go into the decisions concerning the use of various radiation options considered while practicing the "art" of radiation therapy. There may be exceptions to what physicians decide to recommend to specific patients, but these "primary preferred" options as listed in this table reflect our typical considerations and our practice habits. It is recognized that for purposes of continuity of care, and presumed clinical equivalence, patients who could be managed appropriately by more than one boost modality, are more likely to be managed via the modality favor by the "clinical lead" radiation oncologist as listed above.

Reproduced with permission from Halperin E, Wazer DE, Perez CA, et al: *Perez & Brady's principles and practice of radiation oncology,* 7th ed. Philadelphia, PA: Wolters Kluwer; 2019.

A. "Conventional", 3D Conformal (3DCRT), and Intensity-Modulated Radiation (IMRT)

1. Conventional—Conventional external-beam radiation therapy (EBRT) was used in the United States for treating prostate cancer from the late 1960s through the late 1980s (Bagshaw et al, 1988). Placement of the treatment fields was based on bony anatomic landmarks. It is now known that this technique resulted in inadequate coverage of the target volume in nearly one-third of patients. Computed tomography improved our ability to localize and reconstruct pelvic anatomy, allowing more accurate design of treatment portals. According to these studies, the local control rate following "old fashioned" EBRT has been estimated to be between 70% and 90%. The endpoints of these studies were based primarily on a clinical assessment of "local control." These endpoints are now known to underestimate the true incidence of local failures because of the presence of occult cancer in clinically controlled patients.

2. 3DCRT and IMRT—Many of the technical challenges with delivering accurate and high dose radiation have been addressed by the incorporation of (a) computed tomography–assisted localization and reconstruction of the pelvic anatomy in the early 1990s, resulting in 3DCRT; (b) computer optimization algorithms to improve dose conformality in the mid-1990s to create IMRT; and (c) online imaging to create so-called image-guided IMRT or IGRT as the new standard of care for treating clinically localized prostate cancer (Boyer Butler et al, 2001).

B. Image-Guided Radiotherapy (IGRT)

The most common type of IGRT requires the placement of intraprostatic markers typically made of three or more small seeds composed of radiopaque metals by the urologist (Millender et al, 2004; Pouliot et al, 2003; Schiffner et al, 2007; Shinohara and Roach, 2008). These "markers" can be used to adjust for setup (positioning) errors and organ displacement immediately prior to each treatment, as prior to each treatment the therapist acquires an image to compare against the anatomy of the original radiation plan (Shinohara and Roach, 2008). More sophisticated technologies for image guidance have been developed but have not been proven to render better results and are significantly more expensive, and relatively few of them are MRI-compatible (Langen et al, 2003; Willoughby et al, 2006). Because IGRT allows more accurate administration of radiation to the target, less normal tissue receives radiation, and, therefore, fewer side effects are observed (Millender et al, 2004) This may, in turn, permit increased doses of radiation to be given and theoretically lead to improved local control.

▶ Dose-Escalated, Intensity-Modulated, Hypofractionated, and Stereotactic Body Radiation

A. Dose Escalation

Following the early phase I–II studies conducted by the RTOG (9406), higher doses (>70 Gy) became widely accepted as standard among radiation oncologists (Beckendorf et al, 2011; Bolla et al, 2016; Michalski et al, 2012). To date, however, the use of higher doses has resulted only in improved rates of freedom from PSA failure (Beckendorf et al, 2011; Bolla et al, 2016; Dearnaley et al, 2014).

In contrast, the evidence for the use of androgen deprivation therapy (ADT) in conjunction with EBRT appears to be more compelling (Williams et al, 2011; Nanda et al, 2014; Zelefsky et al, 2013; Roach et al, 2012). RTOG 0815 is an ongoing phase III trial attempting to determine whether ADT can be omitted when high doses of radiation are used. An earlier study conducted by the Medical Research Council (MRC) suggests that the use of ADT did not obviate the need for modest dose escalation (Dearnaley et al, 2007). The Spanish trial lead by Zapatero and colleagues similarly supports the need for both dose escalation and ADT (Table 26–2).

Despite the limited evidence for the benefits of radiation dose on outcome (Bekelman et al, 2015), because of an improvement in biochemical control (PSA), high doses are considered standard of care, and NCCN recommends doses of ≤80 Gy at 2 Gy per fraction (Mohler et al, 2010). In order to reduce the duration and cost of treatment, hypofractionated (a modest reduction in the number of treatments) and ultrahypofractionated schedules (dramatic reduction; ie, five or fewer fractions) has become more common and is growing in popularity (Morgan et al, 2019).

B. Hypofractionation

With the advent of IGRT, the accuracy of treatment has improved substantially such that it has become possible to deliver much higher doses of radiation to the prostate with minimal margins, while sparing the surrounding normal tissues and incorporation of image guidance. With hypofractionation, while the cumulative total dose delivered is substantially lowered, the biologically equivalent dose delivered is roughly equivalent or in some cases may be higher. Hypofractionation maximizes patient convenience by shortening the treatment course but also reduces cost to

Table 26–2. General recommendations for radiation therapy and ADT.

Action	Low risk	Favorable intermediate risk	Unfavorable intermediate risk	High risk
Active surveillance	Preferred	In highly selected patients	Appropriate only in those with a short life expectancy	Appropriate only in those with a very short life expectancy
Radiation therapy	PORT	PORT + ADT (4 months)	WPRT + NHT (≥4 months in selected patients	WPRT
ADT	Not indicated	Neoadjuvant and concurrent with EBRT (4 months)	Neoadjuvant (2 months) concurrent ± adjuvant	Neoadjuvant (2 months) and concurrent + adjuvant (24–36 months)
Other				±2nd-generation ADT in selected patients aged < 70 years, node

ADT, Androgen deprivation therapy; PORT, prostate-only radiation therapy; WPRT, whole-pelvic radiation therapy.

Reproduced with permission from Halperin E, Wazer DE, Perez CA, et al: *Perez & Brady's principles and practice of radiation oncology*, 7th ed. Philadelphia, PA: Wolters Kluwer; 2019.

the healthcare system. In addition, hypofractionation has become the standard fractionation method used in a number of European centers and institutions elsewhere (Incrocci et al, 2016; Catton et al, 2017; Lee et al, 2016; Dearnaley et al. 2016; Morgan et al, 2019). The CHIPP trial has made a compelling case that 20 fractions delivered at 3 Gy each can result in outcomes comparable to those of conventionally delivered radiation to 79 Gy. However, it should be noted that as these regimens target the prostate only, it is not clear that it would offer sufficient or appropriate management for patients with high-risk disease who could otherwise be considered for elective pelvic nodal irradiation. Preliminary results do, however, suggest that hypofractionation of pelvic lymph nodes is feasible (Dearnaley et al, 2019).

C. Stereotactic Radiotherapy (SBRT)

An extreme form of hypofractionation is called **stereotactic radiotherapy (SBRT)**, also sometimes referred to as **stereotactic radiosurgery (SRS)** or **stereotactic ablative body radiotherapy (SABR)**. SBRT has become increasingly utilized in the treatment of multiple disease sites in radiation oncology, particularly for definitive treatment of early stage, localized diseases. SBRT in the treatment of prostate cancer typically split into as few as two to five treatments. With this increased target accuracy, SBRT approaches the rapid dropoff in dose achievable with brachytherapy (see discussion below) (Descovich et al, 2013; King et al, 2009; Gonzalez-Motta and Roach, 2017; Kishan et al, 2019a; Morgan et al, 2019).

In addition to definitive management, a number of studies have published promising data based on patients treated with SBRT as a "boost" to the prostate following external beam radiation as a part of dose-escalated radiotherapy (Anwar et al, 2016; Kishan et al, 2018). According to the available published literature, it appears that SBRT results in similar rates of PSA control and kinetics as seen following dose-escalated IMRT or brachytherapy. Table 26–1 summarizes the preferred types of radiation options and relative contraindications used at the University of California San Francisco. Proton and other more exotic forms of external-beam radiation are discussed below.

▶ Other Modalities

A. Brachytherapy

Several forms of external-beam radiation (EBRT) for the treatment of prostate cancer grew in popularity, peaked in the late 1990s, and then plateaued with the development of IGRT and proton- beam radiotherapy (PBRT). The most common alternative form of radiation used to treat prostate cancer is brachytherapy (BT). The major theoretic advantage with BT is its the ability to deliver a very high dose of radiation to a localized area with a decreased number of treatment visits. The use of modern-era imaging techniques for visualizing the placement of radioactive seeds has obviated the need for open surgical procedures. Transrectal ultrasound–guided closed techniques are currently the standard. **Permanent implants** (PPIs) involve the use of low-dose-rate (LD 1R) radiation delivered to a much higher total dose (eg, >100 Gy) (Sahgal and Roach, 2007; Martinez et al, 1990). **Temporary implants** generally involve a lower total dose but at a higher dose rate; hence the term **high-dose-rate (HDR) BT**. An example of an ultrasound-based iodine-125 permanent seed implant of the prostate, performed at our institution, is shown in Figure 26–1. Iodine-125 is the most commonly used isotope, although cesium and palladium are also used.

At selected centers, patients with unfavorable intermediate- and high-risk ratings are treated with a combination of EBRT and interstitial implant with or without hormonal therapy. However, patients with favorable intermediate-risk disease are probably best managed with monotherapy (treatment directed at the prostate only, without ADT). Support for PPI without EBRT can be found in RTOG 0232, which was a randomized trial that demonstrated similar outcomes with PPI BT alone compared to PPT + EBRT (Prestidge et al, 2016). Although proponents of prostate brachytherapy commonly believe that the morbidity associated with interstitial brachytherapy is less than that associated with EBRT, prospective studies using validated quality-of-life instruments suggest that acute morbidity is greater with permanent implants, whereas long-term morbidity tends to be similar (Sanda et al, 2008). PPI combined with EBRT is probably more morbidity-prone than either alone (Prestidge et al, 2016).

External-beam radiotherapy plus brachytherapy (LDR-BT) as a method for dose escalation was compared to dose-escalated EBRT (DE-EBRT) alone in a phase III randomized trial (ASCEND-RT) for unfavorable intermediate-risk and high-risk patients with newly diagnosed prostate cancer. Patients randomized to DE-EBRT were twice as likely to experience biochemical failure compared to the EBRT plus brachytherapy group. However, the cumulative GU toxicity of CTCAEv5 of grade ≥3 (retention requiring catherization or incontinence requiring urinary pads) at 5 years was 18% in the LDR-PB group, threefold higher than in the DE-EBRT group. Fortunately, it appears that at 5 years the rates of grade ≥3 GU toxicity is lower, on average about 8% versus 2% among the two groups, respectively. This study raises an important issue, namely, the degree to which improvement in biochemical control should be valued at the price of decreasing quality of life (Spratt et al, 2018a).

In contrast to the permanent implants, temporary implants (HDR) have the advantage of decreasing radiation exposure to hospital personnel and greater flexibility because of the ability to compensate for less than optimal needle placement (Pellizzon et al, 2003; Anwar et al, 2016). HDR BT traditionally tended to be used for patients with more advanced disease in part because they are usually combined with EBRT and can be used to accurately cover disease that is thought to be outside the gland. Iridium-192 is the only widely used isotope for HDR prostate implants. According to the available data, in the hands of experts, it appears that HDR represents an excellent treatment option and has become increasingly common as the preferred form of brachytherapy (Peach et al, 2016; Dearnaley et al, 2019).

B. Neutrons, Protons, and Heavy-Charged Particles

Particle-beam radiation refers to the use of radiation with higher linear energy transfer than photons or electrons that are used in conventional EBRT. This class of radiation includes neutral heavy particles (eg, neutrons), charged particles (eg, protons), or heavy-charge particles (eg, carbon). The theoretical advantage of proton-based radiotherapy is the potential for a more conformal dose distribution (Peeters et al, 2010; Yu et al. 2013; Coen et al., 2011) Two prospective randomized trials have been completed to date. The first showed a significant improvement in local control in patients with high-grade tumors but no improvement in disease-free, relapse-free, or overall survival (hipley et al, 1995). There was no benefit to other subsets of patients, and the 5-year actuarial rates of rectal bleeding were significantly higher ($p = .002$) with mixed-beam treatment. The second trial essentially confirmed the dose response findings of earlier x-ray–based dose escalation trials with better PSA control for men treated to 79 Gy than those treated to 70 Gy (Zietman et al, 2005)

The attractiveness of heavy particles such as neutron (or carbon) based radiotherapy relates to the relative lack of oxygen dependence. Heavy-charge particles (such as carbon) are thought to have the advantages of both neutrons and protons (greater mass and less lateral scatter, respectively). Early studies using this technology have been encouraging, but the series are small, follow-up is relatively short, and this equipment has limited availability (Forman et al, 2002; Dang et al, 2005; Mizoguchi et al, 2015). A recent update of the carbon experience including more than 2000 patients supports the safety and efficacy (Dearnaley et al, 2019); however, longer follow-up and more studies including randomized trials will be required to definitively determine the impact of these alternative types of radiation on long-term survival (Lazar et al, 2018).

Hormonal Therapy and Radiotherapy

The role of androgen deprivation therapy (ADT), in conjunction with radiation, remains a controversial topic. ADT has been combined with EBRT concurrently, neoadjuvantly (before) and adjuvantly (after) RT to potentiate the oncologic effect of RT. Although there remains no consensus as to exactly who should receive ADT and how long it should continue, the best evidence suggests that low-risk patients do not benefit from ADT, intermediate-risk patients benefit from short-term hormonal therapy, and high-risk patients benefit from long-term hormonal therapy (Ludwig et al, 2015; Zapatero et al, 2015; Bolla et al, 2009; Roach and Thomas, 2012; Roach et al, 2012)

The most commonly used regimen for "short-term" hormonal therapy consists of combined androgen blockade using a luteinizing hormone-releasing hormone agent and an antiandrogen starting 2 months before (neoadjuvant) and lasting for at least 2 months after the start of radiotherapy, for a total of 4 months, appears optimal (Pisansky et al, 2015; Roach et al, 2012).

Patients receiving hormonal therapy appear to benefit from the addition of ADT with or without whole-pelvis radiotherapy if given prior to RT. Interestingly, the long-term outcomes from RTOG 9413 suggest that there appear to be an interaction between timing of ADT and elective pelvic nodal radiation such that patients receiving prostate-only RT benefit more from adjuvant ADT but that WPRT should not be used prior to RT (Roach et al, 2018). Most patients with high-risk disease (T3 GS = 7–10 or GS = 8–10) should also receive long-term adjuvant ADT with a luteinizing hormone-releasing hormone agonist for 2–3 years or longer in selected patients (Jackson et al, 2016; Moul et al, 2011; Bolla et al, 2010; Roach et al, 2012). Table 26–2 summarizes the general conclusions based on results of major phase III trials including short- and long-term ADT and EBRT, respectively. ADT alone is not as effective as ADT combined with EBRT (Warde et al, 2011; Fosså et al, 2016).

A. Postoperative Radiotherapy and Salvage Brachytherapy

1. Postoperative radiotherapy following a radical prostatectomy—The objective of local and regional postoperative radiotherapy is to eliminate microscopic residual tumor in the surgical bed, regional periprostatic tissues, and/or regional lymph nodes. The use of postoperative radiation following surgery is warranted in patients with one or multiple adverse features, which include (a) positive surgical margins, (b) seminal vesicle involvement, (c) lymph node involvement, (d) extracapsular extension, (e) increasing PSA, and (f) biopsy-proven recurrence. Radiotherapy may be administered prior to evidence of a recurrence or so-called adjuvant treatment or after documented failure (usually based on a detectable or rising PSA) or so-called salvage treatment.

Adjuvant EBRT reduces the incidence of local recurrence in patients with postsurgical microscopic residual tumor after radical prostatectomy. Some urologists cite a concern for the risk of complications associated with adjuvant RT that outweighs the benefits as the reason for not referring patients with these features for radiation. While overtreatment should be avoided, this impression is probably an unfortunate consequence of higher historically reported toxicity risks associated with older radiation treatment techniques. More contemporary series suggest that, with modern equipment and 3D-IMRT planning, the incidence of complications is relatively low (Thompson et al, 2009; Ghadjar et al, 2015; Goenka et al, 2011; Pollack et al, 2018). It should be noted, however, that it is important to evaluate the patient's urinary symptoms as postoperative radiotherapy may prevent or limit additional improvement in urinary continence once initiated (Zaffuto et al, 2017).

The major phase III trials have consistently shown a delay in the risk of biochemical and clinical failure, and the trial with the longest follow-up shows a reduction in the mortality associated with adjuvant EBRT compared with delayed treatment (Bolla et al, 2012b; Wiegel et al, 2014; Thompson et al, 2009) It should be noted that with the use of modern ultrasensitive PSAs for postoperative monitoring, the question of the additional benefit from adjuvant versus salvage is being challenged. A long-term update of the largest of these studies (EORTC 22911), which compared adjuvant/early salvage against late salvage, showed only benefits in PSA control but did not show significantly improved rates of distant metastasis or prostate-cancer-specific or overall survival (Bolla et al, 2012a). The findings from these trials are consistent with those of retrospective studies that suggest that patients who are treated early postoperatively before clinically manifesting a local recurrence appear to have improved disease-free survival, time to distant metastasis, and freedom from biochemical relapse, when compared with patients undergoing salvage treatment (Nudell et al, 1999; Valicenti et al, 1999). Only 50% of such patients are successfully treated for biopsy-proven recurrence at 3 years (Rogers Grossfeld et al, 1998).

Salvage radiotherapy is the only curative option in men with biochemical failure after surgery. A nomogram reported by Stephenson colleagues, updated with longer-term follow up, provides a reasonable estimate of the overall effectiveness of men undergoing salvage EBRT for most patients (Tendulkar et al, 2016). Overall, only 25% are long-term disease-free, with some subsets doing substantially better. For example, among those with a pre-EBRT PSA of <0.5 ng/mL, a long doubling time (>6 years), and positive margins but negative seminal vesicles and lymph node,s may achieve a progression-free rate of ≤80% at 6 years when treated with conventional dose radiation and ADT. Importantly, data from the recent update of the Stephenson nomogram suggest that early salvage for rising PSA when the PSA is even less than the AUA definition of post-RRP recurrence (eg, PSA 0.05–0.2) may be beneficial. This comes from the observation that rates of long-term biochemical control is improved in patients with lower presalvage RT PSAs, as the best outcomes are observed in patients with a PSA lower than 0.2, suggesting that there is no minimum threshold to this association (Tendulkar et al, 2016).

Finally, while post-op RT historically has been directly only to the prostate bed as the most common site of recurrence is at the anastomosis, it remains a controversial question as to the benefit of elective nodal irradiation in patients with pathologically negative nodes, particularly in patients with high-risk disease (eg, Gleason score 8+ or pT3+) or those without an adequate lymph node dissection. Retrospective studies have suggested that pelvic lymph nodal treatment may improve outcome compared with ADT alone (Pozzo, Da et al, 2009; Spiotto et al, 2007). Preliminary results from RTOG 0534 support the value of adding pelvic nodal radiation in the salvage setting (Pollack et al, 2018). RTOG 0534 is a phase III randomized trial evaluating whether pelvic nodal RT is beneficial in patients receiving salvage RT to the prostate bed with short-term ADT, and demonstrate a progression-free survival advantage with the addition of comprehensive pelvic nodal irradiation.

Nomograms and genomic classifiers are being used increasingly to predict outcomes and guide management of patients treated in the postprostatectomy setting. However, these studies are confounded by selection bias, a lack of randomization, and the relative short timeframe of 5–10 years for biochemical control and 5 years of metastatic disease (Tendulkar et al, 2016; Den et al, 2015; Spratt et al, 2018b). Clearly, more studies are needed, and with further studies it seems more plausible that these approaches may be most useful for selecting patients who might benefit from more aggressive treatment (Chan and Roach, 2016)

2. Postradiotherapy failure and salvage treatment— Although most patients with disease recurring locally after radiotherapy are managed with ADT or occasionally RP, many of these patients may be candidates for salvage radiotherapy (Kimura et al, 2010; Aaronson et al, 2009; Lee et al, 2007). While the complication rate is quite high in some series (Nguyen et al, 2009), the toxicity rates are likely to be operator- and technique-dependent and may be highly variable because of due the heterogeneity of salvage cases. The RTOG recently conducted a phase I–II trial (RTOG 0526) of brachytherapy salvage of EBRT failures, showing an overall acceptable risk of 14% of grade 3 adverse events and no grade 4/5 toxicities (Crook et al, 2019). It is also possible to perform salvage of either brachytherapy or EBRT failures using SBRT (ASTRO 2018). The rate of GU toxicity following salvage is associated with the issue of whether the reirradiation field is unilateral, sparing the midline (one side of involvement of the gland) or central, crossing the midline (requiring RT to be delivered across the midline). In addition to brachytherapy savage of EBRT failures, brachytherapy may be ideal for selected patients with recurrences after brachytherapy (Hsu et al, 2013).

Finally, contrary to the misconception that patients failing radiation cannot undergo surgery, salvage prostatectomy can be performed. While the complication rates are higher than those in patients without prior radiation, it can be successful with low morbidity with the right patient selection and surgical experience.

B. Complications of Radiotherapy for Prostate Cancer

Most patients experience urinary frequency, urgency, and worsening nocturia during the course of treatment, with occasional to rare urinary retention. Acute GU symptoms responds well to α-1 inhibitors such as tamsulosin (Prosnitz et al, 1999). In patients receiving whole-pelvis irradiation, mild diarrhea may develop, but moderate to severe late complications are similar to those in patients receiving prostate only RT (Pinkawa et al, 2008, 2010). Urinary incontinence is usually associated with a history of a prior transurethral resection of the prostate. Hematuria and ureteral strictures occur in <2–10% of patients and are usually mild and self-limited. Mild, self-limited rectal bleeding occurs in approximately 10% of patients and is dose- and volume-related, while nausea can be a rare side effect related to the superior extent of the field that improves with pharmacologic management. Following conventional EBRT, fecal incontinence is uncommon, but rectal urgency due to reduction in rectal dispensability is observed in 10% of patients (Lukka et al, 2005). While there is concern that addition of pelvic nodal irradiation can increase treatment-related toxicity, retrospective studies have not necessarily show a significant difference (Melotek et al, 2015; Roach, 2018).

The loss of erectile function is a particularly common patient concern, and the most common, long-term complications of radiotherapy appear to be related to dosage and volume (Rivin del Campo et al, 2013). Impotence is reported in 35–40% of patients who were potent before treatment and maybe critically dependent on the dose of radiation received by the bulb of the penis (Roach et al, 2010). One rather large prospective study concluded that sexual dysfunction may be slightly lower after EBRT than after brachytherapy, but both had a lower impact on function than radical prostatectomy or cryosurgery (Sanda et al, 2008). Nevertheless, most patients experience a decrease in the frequency and quality of intercourse after radiation, and most note a decrease in the volume of ejaculate. Potency diminishes further with time owing to both natural aging and late radiation–induced normal tissue injury.

Acute urinary toxicity associated with brachytherapy is more common and longer-lasting than that seen with 3DCRT (Wilt et al, 2008; Mohammed et al, 2010; Rodda et al, 2017; Hsu et al, 2010; Sanda et al, 2008). The incidence of strictures is also higher. Acute obstruction occurs in 2–20% of patients. As shown by results of the ASCEND-RT trial, whereas the cumulative incidence of grade 3+ GU toxicity is higher in brachytherapy patients, at later timepoints, there was no significant difference as compared to patients receiving EBRT only (Rodda et al, 2017). Although incontinence requiring pads is uncommon following radiotherapy, it can occur in up to 50% of patients who have undergone a previous transurethral resection of the prostate. The frequency of rectal toxicity following brachytherapy is generally believed to be less than that with 3DCRT (Sanda et al, 2008; Alexianu and Weiss, 2000) and surgery (Donovan et al, 2016).

NONPROSTATE GENITOURINARY CANCERS

Urinary Tract Tumors

Urothelial cancers (UCs) can occur along the entirety of the urinary tract, from the kidney to the penile urethra. The vast majority of UCs are primary tumors of the bladder, as a majority of these involve the renal pelvis and only 5% originate in the upper urinary tract (Muñoz et al, 2015). The role of radiation therapy in the management of UC varies by tumor location, ranging from a palliative to a definitive intent either alone or in combination with surgery and chemotherapy. The latter type includes cases where RT can offer a dramatically improved quality of life, notably in organ-sparing approaches for the management of muscle-invasive bladder cancer and the management of penile cancer. In this section we will review the common uses of EBRT and brachytherapy in the management of urinary tract malignancies.

Bladder Cancer

In the absence of durable local control, the natural history of bladder cancer is that of progressive growth and invasion with the eventual development of distant metastases. At diagnosis, most patients (85%) with transitional cell carcinoma (TCC) of the bladder have disease that consists of superficial mucosal lesions (Ta, T1). The presence of TCC in situ is associated with a more aggressive natural history, with a higher probability of recurrence and progression to muscle-invasive disease (Wolf et al, 1994). The addition of intravesicle immunotherapy (Bacille Calmette–Guerin [BCG]) or chemotherapy (eg, mitomycin C) decreases the overall recurrence rate by approximately 30%, when compared with TURBT alone (Smith et al, 1999). Nonetheless, within the first 5 years, tumor progression is diagnosed in 20–40% of patients despite this additional treatment (Holmäng et al, 1999; Cheng et al, 1999).

The development of muscle-invasive disease (T2–T4) is accompanied by a significant increase in the incidence of metastatic spread and cause-specific death. Unfortunately, roughly half of the patients diagnosed with muscle-invasive TCC have disseminated disease at time of biopsy, which is often occult at diagnosis. Five-year survival rates of up to 60% are reported for early stages (T1/T2a, N0); however, rates fall to ≤40% for more advanced tumors (T2b/T4, N^+) (Stein and Skinner 2003; Stein et al, 2001; Knap et al, 2003). Late systemic disease recurrence, most frequently pulmonary metastases, with or without local recurrence accounts for the decline in survival, emphasizing the importance of adjuvant cytotoxic chemotherapy (Dalbagni et al. 2001a; Stein et al, 2001a). Following decades of unsuccessful single and bimodality treatments, contemporary management utilizes combinations of cytotoxic chemotherapy, radiotherapy, and/or surgery (also known as "trimodality" treatment) in an attempt to improve survival and, if possible, facilitate organ preservation.

A. EBRT Management of Bladder Cancer

External-beam radiotherapy has had no role in the management of in situ (Tis) or superficial (T1) bladder cancer. Investigators at the University of Erlangen, Germany, proposed a role for post-TURBT EBRT or EBRT with chemotherapy (EBRT/CT, where CT consists of cisplatin or carboplatin with 5-fluorouracil) for high-risk (T1G3, T1G1–2 associated with Tis, multifocality, or tumor diameter >5 cm) or multiple recurrent superficial bladder cancers (Weiss et al, 2006). Eighty-eight percent (121 in 137) of patients treated with EBRT or EBRT/CT 4–6 weeks after initial TURBT were found to have a complete response (CR) at restaging TURBT. Patients not achieving a CR (16 im 137; 12%) were managed with immediate cystectomy. Five- and 10-year DSS and OS rates for patients with CR were 89% and 75% and 79% and 53%, respectively. When the evaluation was limited to patients with T1G3 tumors, 5- and 10-year DSS and OS rates were 80% and 64% and 71% and 47%, respectively. These rates are comparable with those seen in primary cystectomy series in T1 bladder cancer (Honma et al, 2004; Shariat et al, 2006; Amling et al, 1994, 2001). Of note, patients receiving EBRT/CT had significantly higher 5-year DSS rates than did patients treated with EBRT only. These findings are provocative; however, a randomized trial confirming the added benefit of EBRT/CT has not been performed. A phase III randomized trial by Harland and colleagues reported that adjuvant EBRT provided no benefit over observation alone for time to progression, progression-free survival, or OS for T1G3 bladder tumors (Harland et al, 2007).

Many urologic oncologists see the role for radiotherapy in the management of TCC as being limited to patients who are not surgical candidates and are intended as palliation for patients with locally advanced, unresectable tumors (Balar et al, 2011). Many of them believe radical cystectomy (RC) to be the gold standard for management of recurrent superficial and primary muscle-invasive TCC in the United States, despite the absence of robust evidence supporting its superiority (Shipley et al, 2003; Maarouf et al, 2011).

In fact, recent studies suggest that multimodality organ-sparing approaches are comparatively more effective than RC for both men and women with TCCA (Siracusano et al, 2018; Royce et al, 2019). For muscle-invasive TCC, three of four randomized trials comparing EBRT (≤50 Gy) plus immediate cystectomy versus primary EBRT (60 Gy) and delayed (salvage) cystectomy demonstrated equivalent long-term survival rates with either treatment, although one trial demonstrated a significant benefit associated with immediate cystectomy (Balar et al, 2011; Bloom et al, 1982; Shelley et al, 2001; Miller 1977). Of note, however, there appear to be no significant differences in 5- and 10-year survival rates or the rates of development of metastases following delayed or salvage cystectomy, after failure of attempted bladder preservation (Cooke et al, 2000; Horwich et al, 1995; Petrovich et al, 2001).

The use of combined-modality treatment to achieve organ preservation without compromising treatment outcome has become a management approach of choice for many malignancies, including breast, esophageal, laryngeal, and anorectal cancers. Demonstration of equivalent outcomes with salvage surgery has made organ preservation a reasonable and appropriate treatment choice for some patients with muscle-invasive TCC.

B. Combined Modality Management of Muscle-Invasive Bladder Cancer (Transurethral Bladder Resection, Chemotherapy, and EBRT) and Organ Preservation

Bladder preservation therapy provides an alternative treatment option for selected patients with invasive TCC, without compromised survival. Patient selection for bladder-sparing approaches is of prime importance. Patients who would be suitable primary surgical candidates should be considered for this approach, since salvage cystectomy may be indicated. The optimal regimen of combined radiotherapy and chemotherapy remains to be determined.

Numerous prospective randomized trials evaluating combined-modality therapy for bladder preservation have been completed. In general, these trials have followed a common bladder-preservation algorithm including maximal TURBT, followed by induction chemoradiation, with (or without) an assessment of treatment response (Zietman et al, 2003; Shipley et al, 2003). Individuals with clinical CR continued with bladder-sparing therapy; all others were recommended for extirpative surgery. Completeness of TURBT (visibly complete vs not visibly complete) is associated with significantly lower salvage cystectomy rates. Typical results reported from contemporary bladder-sparing trials are summarized in Table 26–3. These results are comparable to those reported from surgical series indicating that the organ preservation series generally include older and less physically fit patients.

Thousands of patients have been enrolled in randomized trials involving various cytotoxic agents and have been evaluated for efficacy and safety when administered with EBRT. The timing of chemotherapy delivery has also been addressed. Concurrent chemoradiation schedules offer higher CR rates compared with sequential administration (Shipley et al, 1998; Coen et al, 2019; Kaufman et al, 2009; Shelley et al, 2001). Combinations of cisplatin-based chemotherapy with 5-fluorouracil (5FU), paclitaxel, or gemcitabine appear well suited for multimodality treatment for tolerability, radiosensitizing, and complementary cell-killing effects (Kaufman et al, 2009; von der Maase, von der et al, 2005). Platinum-based chemotherapy regimens administered concurrently with EBRT were well tolerated and resulted in a significant increase in freedom from distant metastases and OS. However, additional cycles of neoadjuvant chemotherapy were not found to be beneficial with regard to CR rates, metastasis-free survival, or overall survival, and were associated with higher morbidity and mortality (Tester et al, 1993; Eastham et al, 1996; Shipley et al, 1998). Gemcitabine and the taxanes have also demonstrated significant single-agent activity against TCC. Assessment of concurrent cisplatin and paclitaxel with EBRT followed by adjuvant gemcitabine and cisplatin has yielded acceptable toxicity and shown a promising 81% CR rate (Kaufman et al, 2009). For patients achieving a CR to the induction phase of treatment (when a postchemotherapy cystoscopy is used), it is followed by consolidation chemoradiotherapy and yields

Table 26–3. Selected trials and series involving combined modality bladder preservation trials for locally advanced TCCA.

Series (first author, year)	Treatment regimen[a]	CR rate[b]	5-year OS/other endpoints
RTOG 8512 (Shipley, 1987)	CDDP vs EBRT	66%	52%
RTOG 8802 (Tester, 1993)	MCV vs CDDP vs EBRT	75%	51%
Erlangen (Sauer, 1998)	CDDP/Carbo vs EBRT vs EBRT alone	80% vs 57%	69–57% vs 47%
RTOG 8903 (Shipley, 1998)	±neoadj MCV then CDDP vs EBRT	59%	49%
Spain (Arias, 2000)	Neoadj MVAC then CDDP vs EBRT	68%	48%
SWOG (Hussain, 2001)	CDDP vs 5FU vs EBRT	49%	32%/45% (refused surgery)
RTOG 9906 (Kaufman, 2009)	TAX vs CDDP vs bid EBRT	81%	56%
MGH (Efstathiou, 2012)	Various chemo + EBRT post max TURBT	72%	50%/disease-free (64%)
BC 2001 (James, 2012)	EBRT + CT vs EBRT alone	N/A	48 vs 35%/invasive locoregional DFS (77% vs 66%)
RTOG 0233 (Mitin, 2013)	Bid + paclitaxel-CDDP or fluorouracil-CDDP	72% vs 62%	71$ vs 75%/bladder intact (67% vs 71%)
RTOG 8802, 8903, 9506, 9706, 9906, 0233 (Mak, 2014)	Various chemotherapy and EBRT regimen	14% mic at 10 years	57%/DFS 71%
RTOG 0712 (Coen, 2019)	Bid + CDDP/fluorouracil vs qd+ gemcitabine	88% vs 78%	N/A/ ~75% bladder intact survival

[a] All patients underwent TURBT before induction treatment.

Bid – twice daily; Carbo = carboplatin; CDDP = cisplatin; CR rate = complete response rate (at time of postinduction cystoscopy); EBRT = external-beam radiotherapy; 5FU = 5-fluorouracil; GEM = gemcitabine; MCV = methotrexate, cisplatin, vinblastine; mic = muscle-invasive cancer; MVAC = methotrexate, vinblastine, Adriamycin, cisplatin; neoadj = neoadjuvant; OS = overall survival; Pax = paclitaxel; qd = once daily; RTOG = radiation Therapy Oncology Group; TAX =Taxotere; TCCA = transitional cell carcinoma; TMaB, trastuzumab.

long-term, disease-free, overall and metastases-free survival rates equivalent to those achieved with radical cystectomy.

As is shown in Table 26–3, the 5-year survival rates typically exceed 50%, with nearly two-thirds of the surviving patients maintaining a well-functioning bladder. The incidence of cystectomy performed for palliation of treatment-related morbidity is low (Zietman et al, 2001). Overall survival and metastases-free survival rates realized from these organ-preserving strategies approximate those achieved with primary radical cystectomy (Nichols et al, 2000; Stein et al. 2001; Zietman et al, 2003). This finding suggests that overall survival is driven by the presence or absence of occult distant disease at diagnosis. Limited overall survival, driven by high rates of distant metastases, highlights the need to optimize systemic therapy and better select for patients who are likely to benefit from local treatment.

Following chemoradiation, residual tumor will be found in 20–30% of patients at restaging cystoscopy and TURBT. In addition, 20–30% of patients who achieve a CR develop a new or recurrent TCC. Typically, half of these tumors are superficial, and half are muscle-invasive. Persistent and superficial recurrences of TCC are successfully managed with TURBT with or without intravesical chemotherapy. Treatment outcomes for patients with superficial recurrences are comparable with those for patients who achieve a CR. Invasive recurrences are managed with prompt cystectomy. Salvage surgery is not associated with compromise in overall survival (Dunst et al, 2002; Rödel et al, 2002; Zietman et al, 2001). Although no difference in overall survival is seen in patients who subsequently develop a superficial disease relapse, the 5-year survival rate is less for patients with a native bladder than for patients who do not develop a recurrence.

C. Improving Treatment Outcomes

1. Dose escalation/intensification and predictive/prognostic markers—It appears that an EBRT dose–response relationship exists for TCC. The ability to deliver higher radiotherapy doses requires sophisticated treatment planning and delivery techniques that can spare the small bowel and rectum. Anatomy-based, image-guided EBRT has multiple goals, including accurate tumor targeting, safe delivery of higher radiation doses, and minimizing normal tissue toxicity. The importance of image-guided conformal EBRT has been discussed in the section on prostate cancer. Here again, treatment precision, including accommodation for organ motion and patient positioning, is particularly important. As with the prostate and other pelvic malignancies, external pressure from surrounding bowel and rectum, as well as changes in the volume of urine within the bladder, leads to considerable variation in the position of the bladder (Pos et al, 2003;

Langen and Jones, 2001). A technique consisting in fiducial marker placement and real-time imaging has been used and appears promising (Shimizu et al, 2000). With bowel-sparing treatment of TCC, this also preserves the option for later creation of continent diversions for patients who have an incomplete response to induction chemoradiation.

2. Other methods—Other approaches to dose intensification include brachytherapy and **altered fractionation** regimens. However, twice-daily treatment appears to be no more effective when RT was combined with fluororacil–cisplatin or daily gemcitabine in NRG/RTOG 0712 (Coen et al, 2019) Select European centers have used interstitial brachytherapy, usually in addition to EBRT, to treat TCC with reported local control rates of 70–90%, excellent preservation of bladder function, and low treatment-related toxicity. However, in the absence of randomized prospective trials comparing treatment outcome and toxicity, interstitial brachytherapy cannot be considered a standard of care for TCC. As discussed in in the introductory section on the general principles of radiotherapy, dose escalation via altered fractionation schedules enhances the therapeutic ratio by delivering a higher effective radiotherapy dose (Kaufman et al, 2000; Sangar et al, 2005; Hagan et al, 2003; Housset et al, 1993). Aggressive dose-intensified regimens yield higher CR rates albeit at the cost of moderately severe toxicity. Longer follow-up data are needed to comprehensively assess efficacy and safety.

Several studies have evaluated epidermal growth factor receptor (EGFR) and Her-2/neu expression in bladder cancer. Immunohistochemical staining has revealed Her-2/neu over expression in 40–80% of tumors. Data regarding the relationship between expression and treatment response and outcome are conflicting. One report evaluated the use of EGFR and/or Her-2 with chemotherapy and radiotherapy resistance and treatment outcomes (Chakravarti et al, 2005). EGFR expression appears to be a favorable prognostic factor for muscle-invasive TCC and correlates with significantly higher absolute and disease-specific survival ($p < .044$ and $p < .42$, respectively). A trend toward decreased incidence of distant metastases was also associated with EGFR expression. Her-2 expression was significantly correlated with reduced response rates to chemoradiation. Unlike the findings of other studies, p53 and p16 expression levels had no prognostic significance (Muro, del et al. 2004). In vitro, a synergistic effect between EGFR and ionizing radiation has been shown to increase apoptosis when compared with EGFR alone (Maddineni et al, 2005). The potential diagnostic and therapeutic implications of these findings remain to be clarified. Recent studies suggest that the immune system may play a key role in determining patient outcomes (Efstathiou et al, 2019). Refinements in patient selection by incorporation of biomarkers is a promising area of research that awaits validation in prospective randomized trials (Forker et al, 2015; Choudhury et al, 2010).

D. Toxicity of Radiotherapy Treatment for Bladder Cancer

Treatment-related toxicities during and after chemoradiation primarily affect the bladder, rectum, and small bowel. Acute enteritis and cystitis are frequent complaints occurring in most patients. These are usually mild and are managed symptomatically. Severe marrow-related toxicity is reported in ≤10% of organ preservation patients. Rates of chronic bladder dysfunction of up to 10% have been reported, but symptomatic reduction in the bladder capacity is rare (Fokdal et al, 2004; Rödel et al, 2002; Efstathiou et al, 2012). Chronic, moderately severe rectal and small-bowel injuries are reported in 3–4% and 1–2%, respectively and grade 5 mortality rates are ≤1% (Lee et al, 2014). With more widespread use of conformal radiotherapy techniques, continued declines in toxicity may be anticipated.

Cancers of the Kidney, Renal Pelvis, and Ureter

In the past, EBRT has had limited use in the management of primary renal cell carcinoma (RCC). There are new data on the use of advanced techniques that make radiation therapy and up-and-coming modality in the treatment of RCC. In vivo and in vitro experiments have demonstrated variable though low radiosensitivity to conventionally fractionated EBRT (Ning et al, 1997; Altoos et al, 2015; Zhu et al, 2012) Randomized trials have failed to show a survival or relapse-free survival benefit from preoperative or postoperative radiotherapy (Werf-Messing, van der et al, 1982, 1988; Spera et al, 1988, n.d.; Aref, et al, 1997; Rost and Brosig, 1977; Kjaer et al, 2009). More contemporary retrospective studies with better patient selection and using contemporary EBRT techniques have suggested a benefit of postoperative EBRT in select patients with a high-risk of local-regional failure (T3a and T3c) (Spera et al, 1988, n.d.; Aref et al, 1997; Parashar et al, 2014). Stereotactic body radiotherapy (SBRT) is capable of delivering high-dose radiation per fraction to kidney tumors and appears to overcome any potential radioresistance of RCC. Initial studies using SBRT on primary RCC tumors in nonsurgical patients have shown a reasonable rate of local control (Amini et al, 2015; Sheehan et al, 2003; Teh et al, 2007; Smith et al, 2018)

Similarly, scant data exist supporting a benefit from EBRT for renal pelvis or ureteral carcinoma. Some studies have shown a local control benefit from postnephroureterectomy irradiation in T3–T4, N0, or node-positive patients (Nikolaev and Benda, 2016; Amini et al, 2015; Chen et al, 2011). A role exists for palliative EBRT for metastatic renal cell renal pelvis and ureteral carcinomas (Nikolaev and Benda, 2016). Palliative radiotherapy is effective at relieving pain from bone metastases, palliation of neurologic sequelae from brain metastases, spinal cord and nerve root compression, or invasion (Chen et al, 2011; Ganju et al, 2018; Teh et al, 2007).

SBRT has also been used with a high degree of success in the palliation of intracranial and extracranial metastases from RCC (Smith et al, 2018; Sheehan et al, 2003; Amini et al, 2015; Nguyen et al, 2010).

URETHRAL CANCERS

Primary urethral cancers are very rare in both men and women. The National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database in the United States identified only 1615 cases in the time period between 1973 and 2002 (Swartz et al, 2006). As a result, knowledge regarding risk factors is extremely limited, and no consensus exists regarding optimal management. Squamous cell histologies appear to be the most common, followed by adenocarcinoma and TCC (Grigsby, 1998; Swartz et al, 2006). Distal or anterior lesions appear to have a more favorable prognosis than proximal or posterior lesions (DiMarco et al, 2004; Eng et al, 2003).

Cancer of the Female Urethra

Urethral adenocarcinoma comprises less than 1% of all urogenital tract cancers in women, and retrospective analyses using the SEER database indicate that the annual age-adjusted incidence is less than 5 per 1.5 per million (Swartz et al, 2006; Dayyani et al, 2014). The treatment strategy for each patient is based largely on tumor size and location; however, prognosis remains relatively poor, regardless of treatment approach (DiMarco et al, 2004; Grigsby, 1998; Eng et al, 2003).

Surgical excision has been used for small lesions of the distal urethra with limited success (DiMarco et al, 2004). Both EBRT and brachytherapy are alternatives to surgical resection of early-stage urethral cancers measuring <1 cm in size. For larger lesions, or lesions that extend into surrounding structures, preoperative EBRT radiation to the inguinal, external iliac, and hypogastric nodes is recommended (Grigsby, 1998). Doses of 45–50 Gy are delivered to clinically uninvolved nodes, with an additional 10–15 Gy boost to any involved nodes. A total dose of 60–70 Gy is delivered to the tumor through reduced fields.

Tumors involving the posterior urethra often involve the bladder and have a high incidence of nodal involvement. Locally advanced tumors may be managed with preoperative radiotherapy and exenteration (Dalbagni et al, 2001). If feasible, early lesions may be treated with surgical resection and postoperative EBRT or EBRT alone, and in some series, brachytherapy is utilized in combination with EBRT (Kuettel et al, 1997; Bagshaw et al, 2015; Grigsby, 1998). Local control rates of 20–30% and correspondingly low 5-year survival rates are noted. Preoperative EBRT doses are typically in the range of 45–50 Gy. Definitive and postoperative doses deliver 45–50 Gy to the pelvis and clinically uninvolved nodes, with an additional 10–15 Gy boost to involved nodes. A total dose of 60 Gy is delivered to the entire surface of the vaginal mucosa, and brachytherapy is employed to deliver a final dose of 70–80 Gy to the primary tumor (Libby et al, 2010; Chen et al, 2011; Parisi et al, 2007; Grigsby, 1998). For patients with locally advanced disease, aggressive treatment with multimodality approaches have been utilized with some success (Nicholson et al, 2008).

Urethral strictures are the most frequently reported complication of radiotherapy treatment. Urinary incontinence, cystitis, and vaginal atrophy and stenosis may also occur. Fistulas and small-bowel obstruction due to radiation or tumor necrosis are uncommon (Sharma et al, 2016; Magnuson et al, Shaves 2011).

Cancer of the Penis and Male Urethra

Surgery has been the primary management choice for penile cancer. Although quite effective, neither a partial nor a total penectomy is a desirable therapeutic choice, particularly in terms of patient quality of life. A number of studies have shown significantly increased risk of depression and suicide in men after penectomy (Sarin et al, 1997; Simpson et al, 2018). As the incidence of penile cancer is low, no randomized trials comparing various treatment options has been or is likely to be completed. Given the morbidity associated with penectomy and the high success rates of surgical salvage, in appropriate cases, organ preservation with the use of radiation alone upfront can be considered (Sarin et al, 1997; Delannes et al, 1992; Mazeron et al, 1984; Soria et al, 1997; Ornellas et al, 1994). While the relative paucity of cases has precluded the development of standardized radiotherapy management, it appears that, according to the results of single-institution retrospective analyses and meta-analyses, that a minimum dose of 60–65 Gy is needed for control of the primary tumor (Rozan et al, 1995; Hasan et al, 2015; Sarin et al, 1997). Careful patient selection is important to the success rate of penile preservation; optimal candidates are those with distal, well-differentiated, to moderately well-differentiated tumors that are ≤4 cm in diameter (Hasan et al, 2015; Sarin et al, 1997; Horenblas et al, 1992). While large-scale randomized studies are unlikely to be feasible, meta-analyses suggest that the local control and outcomes are comparable between primary surgery and brachytherapy (Crevoisier, de et al. 2009; Hasan et al, 2015; Sarin et al, 1997; Rozan et al, 1995; Ornellas et al, 1994).

Both EBRT and interstitial brachytherapy may be used to treat penile lesions. If not previously performed, circumcision is required prior to radiotherapy treatment, as inflammation and swelling during treatment can lead to severe phimosis, requiring surgical intervention. Small superficial lesions of the glans and distal shaft may be treated with orthovoltage or low-energy electron beams. Larger, invasive lesions of the penis, penile urethra, and bulbous urethra are managed with EBRT alone or EBRT followed by an interstitial brachytherapy boost. Brachytherapy is required to achieve doses to the primary >65 Gy (Hasan et al, 2015; Cordoba et al, 2016;

Crook et al, 2005; Kellas-Sleczka et al, 2015). Prophylactic irradiation of the bilateral inguinal and pelvic lymph nodes to 45–50 Gy accompanies the management of all except the most superficial primary lesions. Palpable and clinically suspicious nodes receive 65–70 Gy. Local failure rates of 15–37% have been reported (Rozan et al, 1995; Sarin et al, 1997; Rouscoff et al, 2014; Kellas-Sleczka et al, 2015; Soria et al, 1997). In contrast to the above, lesions of the prostatic urethra are managed in a manner similar to that of prostate cancer.

Despite adequate local control rates, the risk of systemic failure associated with urethral tumors results in 5-year survival rates of 55% and 15% for distal and proximal urethral tumors, respectively (Robinson et al. 2018; Salami and Montgomery, 2017; d'Ancona et al, 2004; Crook et al, 2005). Neoadjuvant chemotherapy and radiotherapy, with surgery reserved for salvage, is one strategy for more advanced lesions. Similar to the strategy used for organ preservation in other sites, concurrent chemoradiotherapy has been used for advance lesions (Robinson et al, 2018; Salami and Montgomery, 2017; d'Ancona et al, 2004; Crook et al, 2005).

Regarding **treatment toxicity**, acute, transient sequelae include brisk, moist desquamation of the skin of the penis, urinary frequency, urgency, dysuria, nocturia, and intermittent diarrhea (Crook 2017; Robinson et al, 2018). The risk of soft-tissue necrosis, fibrosis, and phimosis are dose-limiting sequelae for penile irradiation. Urethral and/or meatal stricture is the most common complication of penile and urethral irradiation, and both types of stricture are dosage- and technique-dependent. Symptomatic strictures are managed with urethral dilation, with urethrotomy reserved for severe cases (Dayyani et al, 2014). Although sexual activity is almost uniformly interrupted during the course of treatment, most patients maintain full or slightly diminished potency after radiotherapy.(Dayyani et al, 2014; Cordoba et al, 2016; Simpson et al, 2018)

Testicular Tumors

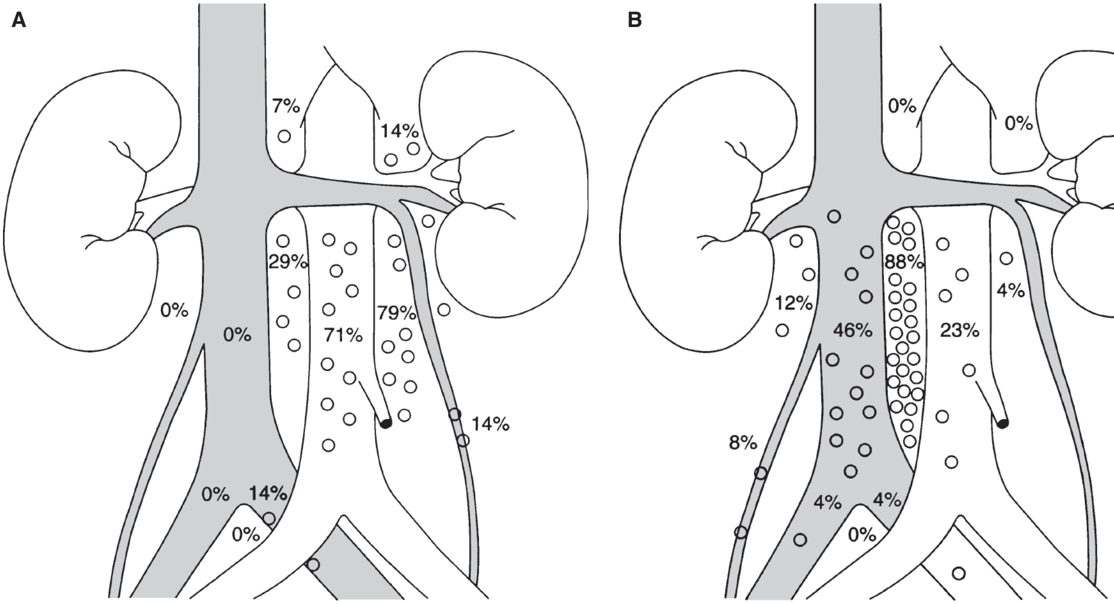
Testicular cancer is the most common malignancy in men aged 15–34 years. For unknown reasons, the incidence of testicular carcinoma has been increasing worldwide, with the greatest increases seen in seminoma. Testicular cancer remains one of the most curable cancers with 5-year relative survival rates of 96–99% for nonmetastatic cases. Chemotherapy plays an important role particularly in early-stage disease as long-term oncologist outcomes are comparable between chemotherapy and radiation, and chemotherapy is tolerated well in younger patients. In addition, there is retrospective evidence suggesting that chemotherapy has a lower rate of secondary malignancy in this young patient population, and RT can be reserved for salvage (Oliver et al, 2011). For example, according to the results from MRC TE19/EORTC 30982, for patients with stage I seminoma, a single cycle of carboplatin had outcomes comparable to those with EBRT. The risk of secondary solid-tumor malignancy is about 10% higher than that of the general population (hazard ratio [HR] 1.8–3.0) (Travis et al, 2005). Other studies, including a major study of patients from the UK and Norway, fail to support a statistically significantly increased risk in secondary malignancies (A Horwich et al. 2014). EBRT has played a primary role in the management of pure seminoma germ cell tumors (GCTs) of the testicles, but predominantly an adjuvant or palliative role in management of **nonseminomatous GCT (NSGCT)**. Furthermore, EBRT has a limited role as palliative therapy in disseminated NSGCT, since patients with brain metastases may still be cured with chemotherapy.

Germ Cell Tumors

Seminoma accounts for 40% of testicular GCTs and occurs in slightly older men (median age, 33 years) than does nonseminoma testicular GCT. Nonseminoma GCTs (embryonal carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed GCT) make up the remaining 60% of testicular tumors, peak at a slightly younger age (median age, 27 years), and are associated with elevations in β-hCG or α-fetoprotein or both in 80% of cases. Radical inguinal orchiectomy with high ligation of the spermatic cord remains the therapeutic mainstay for pure **seminomatous GCTs**, followed by surveillance, radiotherapy, or chemotherapy.

Adjuvant radiotherapy has been used to reduce the risk of local and regional recurrence in ipsilateral pelvic and para-aortic lymph nodes (Chung and Warde, 2011; Felice, De et al, 2016; Aparicio et al, 2005; Jones et al, 2013). Figure 26–4 shows the incidence and location of nodal metastases in early-stage, left- and right-sided testicular tumors. The classic prophylactic postorchiectomy EBRT portals used to reduce the incidence of ipsilateral pelvic and para-aortic nodal recurrences is shown in Figure 26–5A and B. The exquisite radiosensitivity of pure seminoma has permitted progressive reduction in the radiotherapy dose used to treat seminoma, without a reduction relapse-free survival rate (Niewald et al, 1995; Parker et al, 2002; Chung et al, 2004; Horwich et al, 2010; Gürkaynak et al, 2003; Jones et al, 2005). The role for EBRT in the management of pure seminoma has changed greatly over the past 10 years. Since equivalent disease-specific and overall survival rates may be achieved with adjuvant EBRT or surveillance for stage I seminoma (pT1–3, N0, M0, S0), in addition to the absence of treatment-related sequelae and the risk of secondary malignancy, surveillance has become a preferred approach for many centers (Flaquer et al, 2008; Gürkaynak et al, 2003; Chung and Warde, 2011; Warde et al, 2005; Felice, De et al. 2016; Dieckmann et al, 2000).

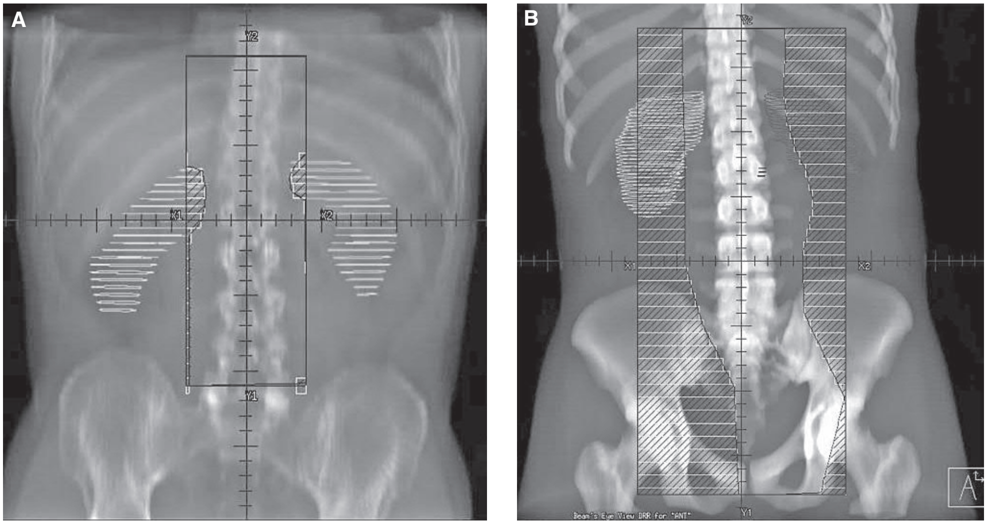
Investigators at Princess Margaret Hospital (PMH) noted an 80–85% 5-year relapse-free rate (RFR) for stage I patients participating in an active surveillance protocol, compared with those undergoing adjuvant EBRT (95–99%) (Warde et al, 2005). Comparable 5-year cause-specific survival rates were achieved with EBRT salvage following surveillance and postorchiectomy EBRT, 99.8% and 100%, respectively.



▲ **Figure 26–4.** ***A:*** **Incidence and location of lymph nodes at risk for an early-stage left-sided testicular seminoma.** ***B:*** **Incidence and location of lymph nodes at risk for an early-stage right-sided testicular seminoma.** (Adapted with permission from Donohue JP, Zachary JM, Maynard BR: Distribution of nodal metastases in nonseminomatous testis cancer, J Urol. 1982 Aug;128(2):315–320.)

The 10-year actuarial risk of requiring chemotherapy salvage was not significantly increased with surveillance.

The primary site of relapse in the surveillance population was determined to be isolated para-aortic lymph nodes (89%). Only 10% of relapses involved pelvic nodal regions. Seventy percent of relapses following prophylactic para-aortic and pelvic nodal EBRT were also found in supradiaphragmatic locations. These findings prompted their conclusion that surveillance should be the standard of care in stage I seminoma (Warde et al. 2002; Leman and Gonzalgo, 2010;



▲ **Figure 26–5.** ***A:*** Para-aortic treatment field ("limited-field") for prophylactic nodal irradiation for stage I testicular seminoma. ***B:*** Pelvic and para-aortic treatment field ("hockey stick or dog-leg") for prophylactic nodal irradiation for stage I testicular seminoma.

Boormans et al, 2017; Parker et al, 2002). However, until recently, surveillance had not been widely accepted as a management standard. A pattern-of-care study evaluating treatment practices at hospital centers in Canada and the United States showed significant variations in practice patterns (Choo et al, 2002). In addition, not all patients choose postorchiectomy observation, nor are all patients suitable candidates for surveillance protocols. Patients who are not compliant and patients with pathologic features, who are associated with significantly higher recurrence rates including tumors >4 cm, rete testis invasion, lymphovascular space invasion, and age ≤33 years, may not be ideal candidates for surveillance (Warde et al, 2002; Leman and Gonzalgo, 2010; Boormans et al, 2017; Parker et al, 2002). Additional considerations are the long-term side effects of frequent radiographic examinations over several years and the cost associated with surveillance. The surveillance guidelines for stage I testicular seminoma are summarized in Table 26–4.

The pattern of recurrence following surveillance and prophylactic EBRT spurred investigations of use of smaller treatment fields, targeting the para-aortic nodes and omitting treatment of the pelvic nodes (limited-field irradiation; Figure 26–5A), including a randomized trial by the MRC. Relapse-free survival rates using limited-field EBRT were equivalent to those seen with classic "dog-leg" irradiation, and hematologic, gastrointestinal, and gonadal toxicity were reduced. Pelvic nodal recurrences, however, were higher with limited-field EBRT (Rowland, 2005; Niazi et al, 2005; As, van et al, 2008; Horwich et al, 2010; Classen et al. 2004; Paly et al, 2013; Martin et al, 2007). Patients who elect limited-field EBRT should probably have pelvic surveillance for a minimum of 10 years as a component of their treatment plan. Pelvic nodal recurrences are readily salvaged with EBRT or chemotherapy (Paly et al, 2013; Martin et al, 2007; As, van et al, 2008). In addition to the benefit of reduced treatment portals, it is reasonable to assume that increased use of IMRT will lead to further reductions in acute EBRT-related toxicity, but the long-term impact on the risk of second cancers is uncertain.

The greatest change in the management of stage I seminoma has been the use single agent carboplatin. Five phase II trials conducted in Europe assessed relapse-free survival rates with two cycles of postorchiectomy, with adjuvant carboplatin. With follow-up ranging from 14 to 74 months, relapse rates were <1% and grades 3–4 hematologic toxicities were <5%. The MRC conducted a prospective phase III trial that randomized men with stage I seminoma to 20–30 Gy limited-field (para-aortic nodal) or large-field (pelvis and para-aortic nodal irradiation) EBRT or one cycle of adjuvant carboplatin (AUC × 7) (Dieckmann et al, 2000, 2016; Aparicio et al, 2005; Germà-Lluch et al, 2002; Steiner et al, 2011; Reiter et al, 2001; Classen, et al. 2004; Oliver et al. 2005). At 4 years' median follow-up, the results indicated that single-cycle carboplatin was noninferior to prophylactic nodal irradiation; relapse-free survival rates were equivalent, patients receiving carboplatin were less likely to take time off from work, and significantly fewer secondary tumors were reported (Oliver et al, 2005; Dieckmann et al, 2016).

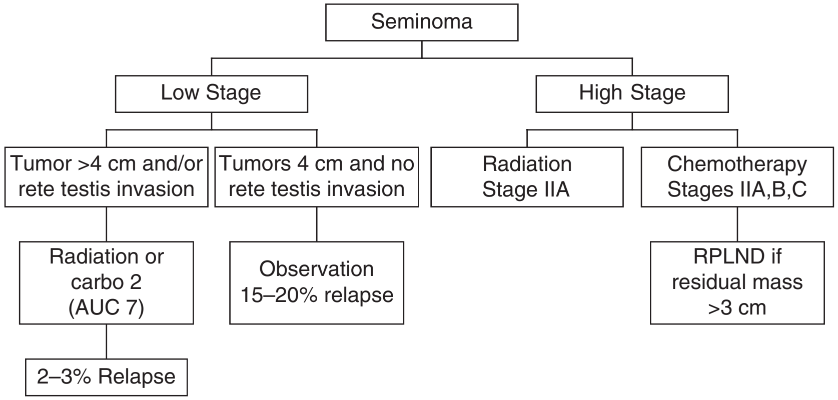
With an absence of consensus regarding treatment for stage I seminoma, the Spanish Germ Cell Cooperative Group developed a risk-adapted management strategy (Figure 26–6) (Aparicio et al, 2005). In 2010, the NCCN published new

Table 26–4. Studies examining outcomes following surveillance for stage I testicular cancer.[a]

Study	Patients	Management after orchiectomy	Findings
Warde et al. (JCO, 2002); retrospective	638	Surveillance; median follow-up 7 years	Relapses in 19% Risk factors for relapse: tumors >4 cm, and invasion of rete testis (although risk factors were not validated in subsequent analysis by Chung (ASCO, 2010, abstract 4535)
Mortenson et al (Eur Urol, 2014), retrospective	1954	Surveillance, then salvage for relapse; median follow-up 15.1 years	Relapses in 18.9% patients, 73% within first 2 years; 62% relapses treated w/RT, 36% treated w/ chemo; disease-specific survival (DSS) at 15 years = 99.3%. Relapse risk factors: tumor size, vascular invasion, epididymal invasion
Kollmannsberger et al. (JCO, 2015), retrospective	2483 (54% seminoma)	Surveillance, then salvage for relapse; median follow-up 5.2 years	Relapse in 13% of seminomas, 92% within 3 years; relapse in 19% nonseminomas, 90% within 2 years; all relapses treated with chemo or RT; 5-year DSS = 99.7%
SGCCG (Aparicio, Ann Oncol 2014)	744	Low-risk— surveillance; high-risk—carboplatin × 2c; median follow-up 6.7 years	Surveillance for low-risk patients; relapse 14.8% overall (8.3% if tumor <4 cm and no rete testis involvement); 5-year CSS 100% with salvage chemo (95%) or RT (5%)

[a] Histologies are seminoma unless otherwise noted.

Reproduced with permission from Hansen EK, Roach M. *Handbook of Evidence-Based Radiation Oncology,* 3rd ed. Chicago, IL: Springer; 2018.


Seminoma
Low Stage
High Stage
Tumor >4 cm and/or rete testis invasion
Tumors 4 cm and no rete testis invasion
Radiation Stage IIA
Chemotherapy Stages IIA,B,C
Radiation or carbo 2 (AUC 7)
Observation 15–20% relapse
RPLND if residual mass >3 cm
2–3% Relapse

▲ **Figure 26–6.** Risk-adapted strategy for the management of stage I seminoma.

practice guidelines for the management of testicular seminoma (http://www.nccn.org) incorporating the data from the contemporary seminoma trials. The impetus for these treatment recommendations appears to be the judicious use of adjuvant therapy in patients with significant risk of disease relapse. In so doing, the late toxicities associated with chemotherapy and radiotherapy may be reduced or avoided. A number of large-center, long-term experiences have supported the use of routine and close observation in place of multimodality or more aggressive therapeutic regimens with minimal to no determinant to long-term overall survival and quality of life because of the effectiveness of salvage therapeutic options and reduced morbidity of treatment-related complications and adverse effects (Germà-Lluch et al; 2002; Dieckmann et al, 2016; Steiner et al, 2011; Horwich et al, 2010; Jones et al. 2013). Treatment recommendations and considerations by stage for seminomas are listed in Table 26–5.

The use for adjuvant postorchiectomy EBRT in **stage II seminoma** (pT1–3, N1–3, M0, S0–1*)* is determined by the bulk of the retroperitoneal lymphadenopathy. Stage IIA (single or multiple nodes all ≤2 cm) and IIB (single or multiple nodes 2–5 cm) patients are successfully treated with EBRT directed to the para-aortic and ipsilateral pelvic lymph nodes, using the so-called hockey stick or dog-leg fields (Figure 26–5B). Doses of 20–30 Gy to the pelvis and para-aortic nodes followed by a 5–10-Gy boost to bulky nodes yield 5-year and 10-year relapse-free, cause-specific, and overall survival rates of 85%, 94%, and 93%, respectively (Ahmed and Wilder, 2015; Giannatempo et al, 2015; Chung et al, 2004; Classen et al, 2003, 2004; Rowland, 2005). Heterogeneity within clinical stages IIA and IIB seminoma due to the presence of one versus multiple nodal masses has led to the suggested use of single-agent carboplatin with EBRT, particularly for stage IIB seminoma (Domont et al, 2013; Horwich et al, 2006, 2013; Chung et al, 2004; Patterson et al, 2001). Patients with bulky retroperitoneal nodal disease (≥5 cm, stage IIC) have high rates of distant relapse. Standard of care is three cycles of cisplatin–etoposide and bleomycin (PEB) or four cycles of etoposide and cisplatinum, followed by surveillance. Residual disease <3 cm may be closely observed, treated with radiotherapy, or surgically resected. Masses measuring ≥3 cm should be resected. Prophylactic mediastinal irradiation for stage II seminoma has long been abandoned. Supradiaphragmatic recurrence rates approximate 3% and may be successfully salvaged with multiagent chemotherapy. EBRT has no role in the primary management of stages IIC, III, and IV seminoma (Horwich et al, 2006, 2010).

Toxicity from Radiotherapy Treatment of Testicular Seminoma

Treatment-related toxicity associated with pelvic and para-aortic EBRT is primarily gastrointestinal in nature and can be easily managed. The most common sequelae may include nausea, diarrhea, rectal urgency, peptic ulcer disease, gastroesophageal reflux disease (GERD), and transient reduction in spermatogenesis (Garcia-Serra et al, 2005; Joos et al, 1997). It has been estimated that 50% or more of the men diagnosed with testicular cancer have impaired spermatogenesis at the time of diagnosis, complicating precise characterization of EBRT effects on fertility (Nalesnik et al, 2004; Huyghe et al, 2004). The severity and duration of oligospermia appear to be dose-related, and testicular scatter doses are thought to be responsible for fertility disturbances. Radiation-related disturbances in spermatogenesis can be minimized by maintaining scatter doses to <20 cGy and the use of smaller treatment (Joos et al, 1997; Huyghe et al, 2004; Haugnes et al, 2012). This is readily achieved with contemporary treatment approaches. Patients treated with postorchiectomy EBRT have a >50% chance of regaining normal spermatogenesis, and all patients regain at least some spermatogenesis, usually within 1–2 years after completing treatment (Hahn et al, 1982; Haugnes et al,

Table 26–5. Treatment recommendations for seminoma.

Stage	Recommended treatment
All patients	Radical inguinal orchiectomy with high ligation of spermatic cord
I seminoma	Postresection: surveillance preferred for pT1–T3 for compliant patients (relapse rate 16%); alternatively, RT (20 Gy to paraaortic ± pelvic LN) or carboplatinum × 1–2c
IIA/IIB seminoma	RT 20 Gy to pelvic and paraaortic LN with boost to gross disease (30 Gy for IIA, 36 Gy for IIB), or primary chemotherapy with etoposide/cisplatin (EP) chemo × 4c or bleomycin/, etoposide/cisplatin (BEP) × 3c.
IIC/D and III seminoma	Chemo: EP × 4c or BEP × 3c
NSGCT	IA: open nerve-sparing retroperitoneal LN dissection (nsRPLND) or surveillance in compliant patients IB: nsRPLND or BEP × 1-2c or surveillance if T2 and compliant patient IS: EP × 4c or BEP × 3c IIA: if markers negative, nsRPLND or EP × 4c or BEP × 3c; if persistent tumor marker elevation, EP × 4c or BEP × 3c IIB: if markers negative and LN metastases within drainage sites, nsRPLND or EP × 4c or BEP × 3c; if persistent tumor marker elevation or multifocal LN methods with aberrant drainage, EP × 4c or BEP × 3c IIC/IIIA: EP × 4c or BEP × 3c IIIB: BEP × 4c IIIC: BEP × 4c or etoposide/ifosfamide/cisplatin (VIP) × 4

Reproduced with permission from Hansen EK, Roach M. *Handbook of Evidence-Based Radiation Oncology,* 3rd ed. Chicago, IL: Springer; 2018.

2012; Huyghe et al, 2004). The existence of severe disturbances in spermatogenesis late in the post-EBRT course probably results from impaired pretreatment sperm cell production and less so the impact of scatter radiation on the remaining testicle.

A small but measurable increase in the risk of second malignancies after a 10–20-year latent period has been reported (Groot et al, 2018; Boujelbene et al, 2011; Horwich et al, 2014), related to radiotherapy but also to chemotherapy with cisplatin-containing agents (Horenblas et al, 2007; Groot et al, 2018). In some reports, the overall observed incidence of second nonseminomatous malignancy was not significantly increased when compared with the expected incidence (Chao et al, 1995). Newer reports have suggested that the use of protons may reduce the risk of radiation-related secondary malignancies (Hoppe et al, 2013; Simone et al, 2012).

SUMMARY

Therapeutic radiation has an extensive history in the management of genitourinary (GU) malignancies. Major advances have been made in its use, particularly for prostate cancer, muscle-invasive transitional cell carcinoma of the bladder, and testicular seminoma, and a continued role for radiation therapy in the multidisciplinary management of genitourinary malignancies seems certain. Overall treatment outcomes continue to improve, accompanied by diminishing rates of toxicity. With continued technologic development, including the use of adaptive radiotherapy, the discovery and application of novel treatment agents, and the combined efforts of each discipline within urologic oncology, patients with GU tumors have greater opportunities to become and remain disease-free.

BIBLIOGRAPHY

Aaronson DS, et al: Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. BJU Int 2009;104(5):600–604. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19245439.)

Ahmed KA, Wilder RB: Stage IIA and IIB testicular seminoma treated postorchiectomy with radiation therapy versus other approaches: A population-based analysis of 241 patients. Int Braz J Urol 2015;41(1):78–85. (Available online at: https://doi.org/10.1590/S1677-5538.IBJU.2015.01.11.)

Ahmed M, et al: Common genetic variation associated with increased susceptibility to prostate cancer does not increase risk of radiotherapy toxicity. Br J Cancer 2016;114(10):1165–1174. (Available online at: https://doi.org/10.1038/bjc.2016.94.)

Alexianu M, Weiss GH: Radical prostatectomy versus brachytherapy for early-stage prostate cancer. J Endourol 2000;14:325–328. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10910147.)

Allen CP, et al: DNA damage response proteins and oxygen modulate prostaglandin E2 growth factor release in response to low and high LET ionizing radiation. Front Oncol 2015;5:260. (Available online at: https://doi.org/10.3389/fonc.2015.00260.)

Altoos BM, et al: Is RCC truly radioresistant? Local control rates of metastatic renal cell carcinoma (RCC) to the lung using stereotactic radiotherapy (SBRT). J Clin Oncol 2015;33(7 Suppl):445–445. (Available online at: https://doi.org/10.1200/jco.2015.33.7_suppl.445.)

Amini A, et al: Local control rates of metastatic renal cell carcinoma (RCC) to the bone using stereotactic body radiation therapy: Is RCC truly radioresistant? Pract Radiat Oncol 2015;5(6):e589–e596. (Available online at: https://doi.org/10.1016/J.PRRO.2015.05.004.)

Amling CL: Diagnosis and management of superficial bladder cancer. Curr Problems Cancer 2001;25(4):219–278. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11514784; accessed 3/30/19.)

Amling CL, Thrasher JB, Frazier HA, Dodge RK, Robertson JE, Paulson DF: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 1994;151(1):31–35; discussion 35–36. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/8254828.)

Andreassen CN, et al: Individual patient data meta-analysis shows a significant association between the ATM Rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. Radiother Oncol 2016;121(3):431–439. (Available online at: https://doi.org/10.1016/j.radonc.2016.06.017.)

Anwar M, Weinberg V, Seymour Z, Hsu IJ, Roach M, Gottschalk AR: Outcomes of hypofractionated stereotactic body radiotherapy boost for intermediate and high-risk prostate cancer. Radiat Oncol 2016;11(1):1–8. (Available online at: https://doi.org/10.1186/s13014-016-0585-y.)

Aparicio J, et al: Risk-adapted management for patients with clinical stage I seminoma: The Second Spanish Germ Cell Cancer Cooperative Group Study. J Clin Oncol 2005;23(34):8717–8723. (Available online at: https://doi.org/10.1200/JCO.2005.01.9810.)

Aparicio J, Maroto P, Sastre J, Germà JR, behalf of the Spanish Germ Cell Cancer Group on. Re: Mette Saksø Mortensen et al: A Nationwide Cohort Study of Stage I Seminoma Patients Followed on a Surveillance Program. Eur Urol 2014;66:1172–1178.

Arcangeli G, Saracino B, Gomellini S, Petrongari MG, Arcangeli S, Sentinelli S, et al: A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2010;78(1):11–18. (Available online at: https://doi.org/10.1016/j.ijrobp.2009.07.1691.)

Aref I, Bociek RG, Salhani D: Is post-operative radiation for renal cell carcinoma justified? J Eur Soc Ther Radiol Oncol 1997;43(2):155–157. (Available online at: https://doi.org/10.1016/S0167-8140(97)01949-X.)

Arias F et al: Chemoradiotherapy for muscle invading bladder carcinoma. Final report of a single institutional organ-sparing program. Int J Radiat Oncol Biol Phys 2000;47:373–378.

As NJ van, et al: Evidence-based pragmatic guidelines for the follow-up of testicular cancer: Optimising the detection of relapse. Br J Cancer 2008;98(12):1894–1902. (Available online at: https://doi.org/10.1038/sj.bjc.6604280.)

Azria D, et al: Data-based radiation oncology: Design of clinical trials in the toxicity biomarkers era. Front Oncol 2017;7:83. (Available online at: https://doi.org/10.3389/fonc.2017.00083.)

Bagshaw HP, Williams NL, Huang YJ, Tward JD, Gaffney DK: Palladium interstitial implant in combination with external beam radiotherapy and chemotherapy for the definitive treatment of a female urethral carcinoma. Gynecol Oncol Rep 2015;13:40–43. (Available online at: https://doi.or(g/10.1016/j.gore.2015.06.001.)

Bagshaw MA, Cox RS, Ray GR: Status of prostate cancer at Stanford University. NCI Monogr 1988;7:47–60. (Available online at: http://number.)

Balar A, Bajorin DF, Milowsky MI: Management of invasive bladder cancer in patients who are not candidates for or decline cystectomy. Ther Adv Urol 2011;3(3):107–117. (Available online at: https://doi.org/10.1177/1756287211407543.)

Beckendorf V, et al: 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011;80(4):1056–1063. (Available online at: https://doi.org/10.1016/j.ijrobp.2010.03.049.)

Bekelman JE, et al: Effectiveness of androgen-deprivation therapy and radiotherapy for older men with locally advanced prostate cancer. J Clin Oncol 2015;33(7):716–722. (Available online at: https://doi.org/10.1200/JCO.2014.57.2743.)

Bermudez RS, Izaguirre A, Roach M 3rd: State-of-the-art radiotherapy in the management of clinically localized prostate carcinoma. Future Oncol 2007;3(1):103–111. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17280507.)

Bloom HJ, Hendry WF, Wallace DM, Skeet RG: Treatment of T3 bladder ancer: Controlled trial of pre-operative radiotherapy and radical cystectomy versus radical radiotherapy. Br J Urol 1982;54(2):136–151. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/7044462.)

Bolla M, et al: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC Trial 22911). Lancet 2012a;380(9858):2018–2027. (Available online at: https://doi.org/10.1016/S0140-6736(12)61253-7.)

Bolla M, et al: Duration of androgen suppression in the treatment of prostate cancer. New Engl J Med 2009;360(24):2516–227. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19516032.)

Bolla M, et al: External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11(11):1066–1073. (Available online at: https://doi.org/10.1016/S1470-2045(10)70223-0.)

Bolla M, et al: Short androgen suppression and radiation dose escalation for intermediate-and high-risk localized prostate cancer: Results of EORTC Trial 22991. J Clin Oncol 2016;34(15):1748–1756. (Available at: https://doi.org/10.1200/JCO.2015.64.8055.)

Bolla M, et al: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC Trial 22911). Lancet 2012b;380(9858):2018–2027. (Available online at: https://doi.org/10.1016/S0140-6736(12)61253-7.)

Boormans JL, et al: Testicular tumour size and rete testis invasion as prognostic factors for the risk of relapse of clinical stage I seminoma testis patients under surveillance: A systematic review by the Testicular Cancer Guidelines Panel. Eur Urol 2017;73(3):394–405. (Available online at: https://doi.org/10.1016/j.eururo.2017.09.025.)

Boujelbene N, et al: Pure seminoma: A review and update. Radiat Oncol 2011;6(1):90. (Available online at: https://doi.org/10.1186/1748-717X-6-90.)

Bourgeois DJ 3rd, Kraus S, Maaloof BN, Sartor O: Radiation for bone metastases. Curr Opin Support Palliat Care 2011;5(3):227–232. (Available online at; https://doi.org/10.1097/SPC.0b013e3283499caa.)

Boyer Butler EB, et al: Intensity-modulated radiotherapy: Current status and issues of interest. Intensity Modulated Radiation Therapy Collaborative Working Group. Int J Radiat Oncol Biol Phys 2001;51:880–914. (Available online at: http://number.)

Brenner DJ, Hall EJ: Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 1999;43:1095–1101. (Available online at: http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=10192361.)

Carl J, Rades D, Doemer C, Setter C, Dunst J, Holländer NH: Palliative radiotherapy to dominant symptomatic lesion in patients with hormone refractory prostate cancer (PRADO). Radiat Oncol 2019;14(1):3. (Available online at: https://doi.org/10.1186/s13014-019-1209-0.)

Carroll PH, Mohler JL: NCCN Guidelines updates: Prostate cancer and prostate cancer early detection. J Natl Comprehens Cancer Network 2018;16(5S):620–623. (Available online at: https://doi.org/10.6004/jnccn.2018.0036.)

Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al: Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35(17):1884–1890. (Available online at: https://doi.org/10.1200/JCO.2016.71.7397.)

Chakravarti A, Winter K, Wu C-L, Kaufman D, Hammond E, Parliament M, et al: Expression of the epidermal growth factor receptor and Her-2 are predictors of favorable outcome and reduced complete response rates, respectively, in patients with muscle-invading bladder cancers treated by concurrent radiation and cisplatin-based chemotherapy: A report from the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2005;62(2):309–317. (Available online at: https://doi.org/10.1016/j.ijrobp.2004.09.047.)

Chan J, Roach M: Re: Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. Eur Urol 2016;69(3):539–540. (PAvailable online at: https://doi.org/10.1016/j.eururo.2015.12.026.)

Chao CKS, Lai P, Michalski JM, Perez CA: Secondary malignancy among seminoma patients treated with adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 1995;33(4):831–835. (Available online at: https://doi.org/10.1016/0360-3016(95)00200-8.)

Chen B, Zeng Z-C, Wang G-M, Zhang L, Lin Z-M, Sun L-A, et al: Radiotherapy may improve overall survival of patients with T3/T4 transitional cell carcinoma of the renal pelvis or ureter and delay bladder tumour relapse. BMC Cancer 2011a;11:297. (Available online at: https://doi.org/10.1186/1471-2407-11-297.)

Cheng L, Neumann RM, Weaver AL, Spotts BE, Bostwick DG: Predicting cancer progression in patients with stage T1 bladder carcinoma. J Clin Oncol 1999;17(10):3182–3187. (Available at: https://doi.org/10.1200/JCO.1999.17.10.3182.)

Choudhury A, Nelson LD, Teo MTW, Chilka S, Bhattarai S, Johnston CF, et al: MRE11 expression is predictive of cause-specific survival following radical radiotherapy for muscle-invasive bladder cancer. Cancer Res 2010;70(18):7017–7026. (Available online at: https://doi.org/10.1158/0008-5472.CAN-10-1202.)

Choo R et al: Survey of radiation oncologists: practice patterns of the management of stage I seminoma of testis in Canada and a selected group in the United States. Can J Urol 2002; 9:1479–1485.

Chung P, Warde P: Stage I seminoma: Adjuvant treatment is effective but is it necessary? J Natl Cancer Inst 2011;103(3):194–196. (Available online at: https://doi.org/10.1093/jnci/djq535.)

Chung PWM, Gospodarowicz MK, Panzarella T, Jewett MAS, Sturgeon JFG, Tew-George B, et al: Stage II testicular seminoma: Patterns of recurrence and outcome of treatment. Eur Urol 2004;45(6):754–760. (Available online at: https://doi.org/10.1016/j.eururo.2004.01.020.)

Classen J, Schmidberger H, Meisner C, Winkler C, Dunst J, Souchon R, et al: Para-aortic irradiation for stage I testicular seminoma: Results of a prospective study in 675 patients. A trial of the German Testicular Cancer Study Group (GTCSG). Br J Cancer 2004;90(12):2305–2311. (Available online at: https://doi.org/10.1038/sj.bjc.6601867.)

Classen J, Schmidberger H, Meisner C, Souchon R, Sautter-Bihl M-L, Sauer R, et al: Radiotherapy for stages IIA/B testicular seminoma: Final report of a prospective multicenter clinical trial. *J Clin Oncol* 2003;21(6):1101–1106. (Available online at: https://doi.org/10.1200/JCO.2003.06.065.)

Coen JJ, Zietman AL, Rossi CJ, Grocela JA, Efstathiou JA, Yan Y, et al: Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: A case-matched analysis. Int J Radiat Oncol Biol Phys 2011. (Available online at: https://doi.org/S0360-3016(11)00206-9 [pii]10.1016/j.ijrobp.2011.01.039.)

Coen JJ, Zhang P, Saylor PJ, Lee CT, Wu C-L, Parker W, et al: Bladder preservation with twice-a-day radiation plus fluorouracil/cisplatin or once daily radiation plus gemcitabine for muscle-invasive bladder cancer: NRG/RTOG 0712—a randomized phase II trial. J Clin Oncol 2019;37(1):44–51. (Available online at: https://doi.org/10.1200/JCO.18.00537.)

Cooke PW, Dunn JA, Latief T, Bathers S, James ND, Wallace DMA: Long-term risk of salvage cystectomy after radiotherapy for muscle-invasive bladder cancer. Eur Urol 2000;38(3):279–286. (Available online at: https://doi.org/10.1159/000020294.)

Cordoba A, Escande A, Lopez S, Mortier L, Mirabel X, Coche-Déqueant B, et al: Low-dose brachytherapy for early stage penile cancer: A 20-year single-institution study (73 patients). Radiat Oncol (London) 2016;11:96. (Available online at: https://doi.org/10.1186/s13014-016-0676-9.)

Crevoisier R de, Slimane K, Sanfilippo N, Bossi A, Albano M, Dumas I, et al: Long-term results of brachytherapy for carcinoma of the penis confined to the glans (N- or NX). Int J Radiat Oncol Biol Phys 2009;74(4):1150–1156. (Available online at: https://doi.org/10.1016/j.ijrobp.2008.09.054.)

Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdolell M: Postradiotherapy prostate biopsies: What do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys 2000;48:355–367. (Available online at: http://www.sciencedirect.com/science?*ob=GatewayURL&*origin=CDL&*urlversion=3&*method=citationSearch&*volkey=03603016%2348%23355&*version=1&md5=01e1aeb7f7a4359367aff1933b011bf3.)

Crook J: Radiotherapy approaches for locally advanced penile cancer. Curr OpiniUrol 2017;27(1):62–67. (Available online at: https://doi.org/10.1097/MOU.0000000000000346.)

Crook JM, Jezioranski J, Grimard L, Esche B, Pond G: Penile brachytherapy: Results for 49 patients. Int J Radiat Oncol Biol Phys 2005;62(2):460–467. (Available at: https://doi.org/10.1016/j.ijrobp.2004.10.016.)

Crook JM, Zhang P, Pisansky TM, Trabulsi EJ, Amin MB, Bice W, et al: A prospective phase 2 trial of transperineal ultrasound-guided brachytherapy for locally recurrent prostate cancer after external beam radiation therapy (NRG Oncology/RTOG-0526). Int J Radiat Oncol Biol Phys 2019;103(2):335–343. (Available at: https://doi.org/10.1016/j.ijrobp.2018.09.039.)

Chung H, Roach M: Principles and Practices of Radiation Oncology. In: Perez C, Brady L, Halperin E, editors. 6th ed., New York: Schmidt-Ullrich RK; Lippincott-Raven Publishers; 2019.

Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr HW, et al: Cystectomy for bladder cancer: A contemporary series. J Urol 2001a;165(4):1111–1116. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11257649.)

Dalbagni G, Donat SM, Eschwege P, Herr HW, Zelefsky MJ: Results of high dose rate brachytherapy, anterior pelvic exenteration and external beam radiotherapy for carcinoma of the female urethra. J Urol 2001b;166(5):1759–1761. (Available at: https://doi.org/10.1016/S0022-5347(05)65669-8.)

Dalela D, Santiago-Jiménez M, Yousefi K, Karnes RJ, Ross AE, Den R, et al: Genomic classifier augments the role of pathological features in identifying optimal candidates for adjuvant radiation therapy in patients with prostate cancer: Development and internal validation of a multivariable prognostic model. J Clin Oncol 2017;35(18):1982–1990. (Available at: https://doi.org/10.1200/JCO.2016.69.9918.)

d'Ancona CAL, Gonçalves de Lucena R, de Oliveira Querne FA, Martins MHT, Denardi F, Netto NR. Long-term followup of penile carcinoma treated with penectomy and bilateral modified inguinal lymphadenectomy. J Urol 2004;172(2):498–501; discussion 501. (Available at: http://www.ncbi.nlm.nih.gov/pubmed/15247713.)

Dang B, Li W, Wang J: Comparison doses of secondary neutron with the heavy ions in a 75-ev/n heavy ion beam. Radiat Prot Dosim 2005;117(4):369–372. (Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16046558.)

Dayyani F, Hoffman K, Eifel P, Guo C, Vikram R, Pagliaro LC, et al: Management of advanced primary urethral carcinomas. BJU Int 2014;114:25–31. (Available online at: https://doi.org/10.1111/bju.12630.)

Dearnaley D, Griffin CL, Lewis R, Mayles P, Mayles H, Naismith OF, et al: Toxicity and patient-reported outcomes of a phase 2 randomized trial of prostate and pelvic lymph node versus prostate only radiotherapy in advanced localised prostate cancer (PIVOTAL). Int J Radiat Oncol Biol Phys 2019;103(3):605–617. (Available at: https://doi.org/10.1016/j.ijrobp.2018.10.003.)

Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al: Escalated-dose versus control-dose conformal radiotherary for prostate cancer: Long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol 2014;15(4):464–473. (Available at: https://doi.org/10.1016/S1470-2045(14)70040-3.)

Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al: Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007;8(6):475–487. (Available online at: https://doi.org/10.1016/S1470-2045(07)70143-2.)

Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP Trial. Lancet Oncol 2016;17(8):1047–1060. (Available at: https://doi.org/10.1016/S1470-2045(16)30102-4.)

Delannes M, Malavaud B, Douchez J, et al: Iridium-192 interstitial therapy for squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys 1992;24:479–483.

del Campo R, Thomas EK, Weinberg V, Roach M 3rd. Erectile dysfunction after radiotherapy for prostate cancer: A model assessing the conflicting literature on dose-volume effects. Int J Impot Res 2013;25(5):161–165. (Available online at: https://doi.org/10.1038/ijir.2013.28.)

Den RB, Yousefi K, Trabulsi EJ, Abdollah F, Choeurng V, Feng FY, et al: Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol 2015;33(8):944–951. (Available at: https://doi.org/10.1200/JCO.2014.59.0026.)

Descovich M, Carrara M, Morlino S, Pinnaduwage DS, Saltiel D, Pouliot J, et al: Improving plan quality and consistency by standardization of dose constraints in prostate cancer patients treated with CyberKnife. J Appl Clin Med Phys 2013;14(5):162–172. (Available at: https://doi.org/10.1120/jacmp.v14i5.4333.)

Dieckmann KP, Brüggeboes B, Pichlmeier U, Küster J, Müllerleile U, Bartels H: Adjuvant treatment of clinical stage i seminoma: Is a single course of carboplatin sufficient? Urology 2000;55(1):102–106. (Available at: http://www.ncbi.nlm.nih.gov/pubmed/10654903.)

Dieckmann KP, Dralle-Filiz I, Matthies C, Heinzelbecker J, Bedke J, Ellinger J, et al: Testicular seminoma clinical stage 1: Treatment outcome on a routine care level. J Cancer Res Clin Oncol 2016;142(7):1599–1607. (Available at: https://doi.org/10.1007/s00432-016-2162-z.)

DiMarco DS, DiMarco CS, Zincke H, Webb MJ, Bass SE, Slezak JM, et al: Surgical treatment for local control of female urethral carcinoma. Urol Oncol Semin Orig Investig 2004;22(5):404–409. (Available at: https://doi.org/10.1016/S1078-1439(03)00174-1.)

Domont J, Massard C, Patrikidou A, Bossi A, de Crevoisier R, Rose M, et al: A risk-adapted strategy of radiotherapy or cisplatin-based chemotherapy in stage ii seminoma. Urol Oncol Semin Orig Investig 2013;31(5):697–705. (Available at: https://doi.org/10.1016/J.UROLONC.2011.04.004.)

Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al: Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. New Engl J Med 2016;375(15):1425–1437. (Available at: https://doi.org/10.1056/NEJMoa1606221.)

Dunst J, Rödel C, Zietman A, Schrott KM, Sauer R, Shipley WU, Bladder preservation in muscle-invasive bladder cancer by conservative surgery and radiochemotherapy. Semin Surg Oncol 2002;20(1):24–32. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11291129; accessed 3/31/19.)

Eastham JA, Scardino PT, et al: Radical prostatectomy for clinical T1 and T2 prostate cancer. In: Volgelzang NJ, Scardino PE, Shipley WU, Coffey DS (eds): Comprehensive Textbook of Genitourinary Oncology. Williams & Wilkins, Baltimore, 1996, pp. 741–758.

Efstathiou JA, Spiegel DY, Shipley WU, Heney NM, Kaufman DS, Niemierko A, et al: Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: The MGH experience. Eur Urol 2012;61(4):705–711. (Available at: https://doi.org/10.1016/j.eururo.2011.11.010.)

Efstathiou JA, Mouw KW, Gibb EA, Liu Y, Wu C-L, Drumm MR, et al: Impact of immune and stromal infiltration on outcomes following bladder-sparing trimodality therapy for muscle-invasive bladder cancer. Eur Urol 2019. (Available online at: https://doi.org/10.1016/j.eururo.2019.01.011.)

Elder JS, Jewett HJ, Walsh PC: Radical perineal prostatectomy for clinical stage B2 carcinoma of the prostate. J Urol 1982;127(4):704–706. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7069835.)

Eng TY, Naguib M, Galang T, Fuller CD: Retrospective study of the treatment of urethral cancer. Am J Clin Oncol 2003;26(6):558–562. (Available online at: https://doi.org/10.1097/01.coc.0000037764.72722.07.)

Felice F De, Musio D, Gravina GL, Marampon F, Tombolini V: Adjuvant radiation therapy in stage I seminoma: 20 years of oncologic results. Oncotarget 2016;7(48):80077. (Available online at: https://doi.org/10.18632/ONCOTARGET.11374.)

Flaquer A, Álvarez A, Sánchez SM: Role of radiotherapy in organ-sparing treatment of seminoma. Clin Transl Oncol 2008;10(10): 679–681. (Available online at: https://doi.org/10.1007/s12094-008-0272-z.)

Fokdal L, Høyer M, Meldgaard P, von der Maase H:. 2004. Long-term bladder, colorectal, and sexual functions after radical radiotherapy for urinary bladder cancer. Radiother Oncol 2004;72(2):139–145. (Available at: https://doi.org/10.1016/j.radonc.2004.05.006.)

Forker LJ, Choudhury A, Kiltie AE: Biomarkers of tumour radiosensitivity and predicting benefit from radiotherapy. Clin Oncol 2015;27(10):561–569. (Available online at: https://doi.org/10.1016/j.clon.2015.06.002.)

Forman JD, Yudelev M, Bolton S, Tekyi-Mensah S, Maughan R: Fast neutron irradiation for prostate cancer. Cancer Metastasis Rev 2002;21(2):131–135. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12465752.)

Fosså SD, Wiklund F, Klepp O, Angelsen A, Solberg A, Damber J-E, et al: Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: Final results of the Scandinavian Prostate Cancer Group-7. Eur Urol 2016. (Available online at: https://doi.org/10.1016/j.eururo.2016.03.021.)

Fowler J, Chappell R, Ritter M: Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50:1021–1031. (Available online at: http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11429230.)

Ganju RG, TenNapel M, Mahan N, Zahra A, Shen X: The efficacy of conventionally fractionated radiation in the management of osseous metastases from metastatic renal cell carcinoma. J Oncol 2018:6384253. (Available online at: https://doi.org/10.1155/2018/6384253.)

Garcia-Serra, Allie M., Robert A. Zlotecki, Christopher G. Morris, and Robert J. Amdur. 2005. "Long-Term Results of Radiotherapy for Early-Stage Testicular Seminoma." *American Journal of Clinical Oncology* 28 (2): 119–24. https://doi.org/10.1097/01.coc.0000143843.08585.ce.

Germà-Lluch JR, Garcia del Muro X, Maroto P, Paz-Ares L, Arranz JA, Gumà J, Alba E, et al: Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: The experience of the Spanish Germ-Cell Cancer Group (GG). Eur Urol 2002;42(6):553–562; discussion 562–563. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/12477650.)

Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: First results of the randomized trial SAKK 09/10. *J Clin Oncol* 2015;33(35):4158–4166. (Available online at: https://doi.org/10.1200/JCO.2015.63.3529.)

Giannatempo P, Greco T, Mariani L, Nicolai N, Tana S, Farè E, et al: Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: A Systematic review and meta-analysis of patient outcomes. Ann Oncol 2015;26(4):657–668. (Available online at: https://doi.org/10.1093/annonc/mdu447.)

Giordano SH, Kuo YF, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS: Limits of observational data in determining outcomes from cancer therapy. Cancer 2008;112(11):2456–2466. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18428196.)

Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al: Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. Eur Urol 2011;60(6):1142–1148. (Available online at: https://doi.org/10.1016/j.eururo.2011.08.006.)

Gonzalez-Motta A, Roach M 3rd: Stereotactic body radiation therapy (SBRT) for high-risk prostate cancer: Where are we now? Pract Radiation Oncol 2017;8(3):185–202. (Available online at: https://doi.org/10.1016/j.prro.2017.11.008.)

Grigsby PW: Carcinoma of the urethra in women. Int J Radiat Oncol Biol Phys 1998;41(3):535–541. (Available online at: https://doi.org/10.1016/S0360-3016(97)00773-6.)

Grimm P, Billiet I, Bostwick D, Dicker AP, Frank S, Immerzeel J, et al: Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int 2012;109(Suppl):22–29. (Available online at: https://doi.org/10.1111/j.1464-410X.2011.10827.x.)

Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst J, de Jong IJ, et al: Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. J Clin Oncol 2018;36(24):2504–2513. (Available online at: https://doi.org/10.1200/JCO.2017.77.4174.)

Gürkaynak M, Akyol F, Zorlu F, Akyurek S, Yildiz F, Atahan IL: Stage I testicular seminoma: Para-aortic and iliac irradiation with reduced dose after orchiectomy. Urol Int 2003;71(4):385–388. (Available online at: https://doi.org/10.1159/000074091.)

Hagan MP, Winter KA, Kaufman DS, Wajsman Z, Zietman AL, Heney NM, et al: RTOG 97-06: Initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. Int J Radiat Oncol Biol Phys 2003;57(3):665–672. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/14529770).

Hahn EW, Feingold SM, Simpson L, Batata M: Recovery from aspermia induced by low-dose radiation in seminoma patients. Cancer 1982;50(2):337–340. (Available online at: https://doi.org/10.1002/1097-0142(19820715)50:2<337::AID-CNCR2820500229>3.0.CO;2-6.)

Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al: 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. New Engl J Med 2016;375(15):1415–1424. (Available online at: https://doi.org/10.1056/NEJMoa1606220.)

Hansen EK, Roach M. Handbook of Evidence-Based Radiation Oncology. Springer, 2018. (Available online at: https://doi.org/10.1007/978-3-319-62642-0.)

Harland SJ, Kynaston H, Grigor K, Wallace DM, Beacock C, Kockelbergh R, et al: A randomized trial of radical radiotherapy for the management of PT1G3 NXM0 transitional cell carcinoma of the bladder. J Urol 2007;178(3):807–813. (Available online at: https://doi.org/10.1016/j.juro.2007.05.024.)

Hasan S, Francis A, Hagenauer A, Hirsh A, Kaminsky D, Traugher B, et al: The role of brachytherapy in organ preservation for penile cancer: A meta-analysis and review of the literature. Brachytherapy 2015;14(4):517–524. (Available at: https://doi.org/10.1016/j.brachy.2015.03.008.)

Haugnes HS, Bosl GJ, Boer H, Gietema JA, Brydøy M, Oldenburg J, et al: Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol 2012;30(30):3752–3763. (Available online at: https://doi.org/10.1200/JCO.2012.43.4431.)

Holmäng S, Hedelin H, Anderström C, Holmberg E, Busch C, Johansson SL: Recurrence and progression in low grade papillary urothelial tumors. J Urol 1999;62(3 Pt 1):702–707. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/10458347.)

Honma I, Masumori N, Sato E, Takayanagi A, Takahashi A, Itoh N, et al: Local recurrence after radical cystectomy for invasive bladder cancer: An analysis of predictive factors. Urology 2004;64(4):744–748. (Available online at: https://doi.org/10.1016/j.urology.2004.05.003.)

Hoppe BS, Mamalui-Hunter M, Mendenhall NP, Li Z, Indelicato DJ: Improving the therapeutic ratio by using proton therapy in patients with stage I or II eminoma. Am J Clin Oncol 2013;36(1):31–37. (Available online at: https://doi.org/10.1097/COC.0b013e3182354b9e.)

Horenblas S, van Tinteren H, Delemarre JF, et al: Squamous cell carcinoma of the penis. II. Treatment of the primary tumor. J Urol 1992;147:1533–1538.

Horenblas S, Hoekstra H, Van Den Belt-Dusebout AW, De Wit R, Gietema JA, Louwman MWJ, et al. Surviving testicular cancer: Relationship aspects view project prospective randomized trial for the evaluation of a theoretical follow-up schedule in cutaneous melanoma patients view project treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 2007;25:4370–4378. (Available online at: https://doi.org/10.1200/JCO.2006.10.5296.)

Horwich A, Dearnaley DP, Sohaib A, Pennert K, Huddart RA: Neoadjuvant carboplatin before radiotherapy in stage IIA and IIB seminoma. Ann Oncol 2013;24(8):2104–2107. (Available online at: https://doi.org/10.1093/annonc/mdt148.)

Horwich A, Pendlebury S, Dearnaley DP: 1000 organ conservation in bladder cancer. Eur J Cancer 1995;31:S208–S209. (Available online at: https://doi.org/10.1016/0959-8049(95)96248-C.)

Horwich A, Fossa SD, Huddart R, Dearnaley DP, Stenning S, Aresu M, et al: Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. Br J Cancer 2014;110(1):256–263. (Available online at: https://doi.org/10.1038/bjc.2013.551.)

Horwich A, Alexander EJ, White IM: Update on management of seminoma. Indian J Urol 2010;26(1):82. (Available at: https://doi.org/10.4103/0970-1591.60451.)

Horwich A, Shipley J, Huddart R: Testicular germ-cell cancer. Lancet (London) 2006;367(9512):754–765. (Available online at: https://doi.org/10.1016/S0140-6736(06)68305-0.)

Housset M, Maulard C, Chretien Y, Dufour B, Delanian S, Huart J, et al:. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: A prospective study. J Clin Oncol 1993;11(11):2150–2157. (Available online at: https://doi.org/10.1200/JCO.1993.11.11.2150.)

Hsu CC, Hsu H, Pickett B, Crehange G, Hsu IC, Dea R, et al: Feasibility of MR imaging/MR spectroscopy-planned focal partial salvage permanent prostate implant (PPI) for localized recurrence after initial PPI for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85(2):370–377. (Available online at: https://doi.org/10.1016/j.ijrobp.2012.04.028.)

Hsu IC, Bae K, Shinohara K, Pouliot J, Purdy J, Ibbott G, et al: Phase II trial of combined high-dose-rate brachytherapy and external beam radiotherapy for adenocarcinoma of the prostate: Preliminary results of RTOG 0321. Int J Radiat Oncol Biol Phys 2010;78(3):751–758. (Available online at: https://doi.org/10.1016/j.ijrobp.2009.08.048.)

Hussain MHA et al: Combination Cisplatin, 5-Fluorouracil And Radiation Therapy For Locally Advanced Unresectable Or Medically Unfit Bladder Cancer Cases: A Southwest Oncology Group Study. J Urol 2001;165:56–61.

Huyghe E, Matsuda T, Daudin M, Chevreau C, Bachaud J-M, Plante P, et al: Fertility after testicular cancer treatments: Results of a large multicenter study. Cancer 2004;100(4):732–737. (Available online at: https://doi.org/10.1002/cncr.11950.)

Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): Final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2016;17(8):1061–1069. (Available online at: https://doi.org/10.1016/S1470-2045(16)30070-5.)

Jabbari S, Weinberg VK, Shinohara K, Speight JL, Gottschalk AR, Hsu IC, et al:. Equivalent biochemical control and improved prostate-specific antigen nadir after permanent prostate seed implant brachytherapy versus high-dose three-dimensional conformal radiotherapy and high-dose conformal proton beam radiotherapy boost. Int J Radiat Oncol Biol Phys 2010;76(1):36–42. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19409729.)

Jackson WC, Schipper MJ, Johnson SB, Foster C, Li D, Sandler HM, et al: Duration of androgen deprivation therapy influences outcomes for patients receiving radiation therapy following radical prostatectomy. Eur Urol 2016;69(1):50–57. (Available online at: https://doi.org/10.1016/j.eururo.2015.05.009.)

Johnson SB, Soulos PR, Shafman TD, Mantz CA, Dosoretz AP, Ross R, et al: Patient-reported quality of life after stereotactic body radiation therapy versus moderate hypofractionation for clinically localized prostate cancer. Radiother Oncol 2016;121(2):294–298. (Available online at: https://doi.org/10.1016/j.radonc.2016.10.013.)

James ND et al: Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer. N Engl J Med 2012;366:1477–1488.

Jones G, Arthurs B, Kaya H, MacDonald K, Qin R, Fairbanks RK, et al. Overall survival analysis of adjuvant radiation versus observation in stage I testicular seminoma. Am J Clin Oncol 2013;36(5):500–504. (Avaiable online at: https://doi.org/10.1097/COC.0b013e318254950a.)

Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, et al: Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: A report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol 2005;23(6):1200–1208. (Available online at: https://doi.org/10.1200/JCO.2005.08.003.)

Joos H, Sedlmayer F, Gomahr A, Rahim HBK, Frick J, Kogelnik HD, et al: Endocrine profiles after radiotherapy in stage i seminoma: Impact of two different radiation treatment modalities. Radiother Oncol 1997;43(2):159–162. (Available online at: https://doi.org/10.1016/S0167-8140(97)00052-2.)

Kaufman DS, Winter KA, Shipley WU, Heney NM, Chetner MP, Souhami L, et al: The initial results in muscle-invading bladder cancer of RTOG 95-06: Phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist 2000;5(6):471–476. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11110598.)

Kaufman DS, Winter KA, Shipley WU, Heney NM, Wallace HJ, Toonkel LM, et al: Phase I-II RTOG Study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. Urology 2009;73(4):833–837. (Available online at: https://doi.org/10.1016/j.urology.2008.09.036.)

Kellas-Sleczka S, Bialas B, Fijalkowski M, Wojcieszek P, Szlag M, Cholewka A, et al: Interstitial HDR brachytherapy for penile cancer: A thirteen-year follow up of 55 patients. Brachytherapy 2015;14:S33. (Available online at: https://doi.org/10.1016/j.brachy.2015.02.239.)

Kerns SL, Dorling L, Fachal L, Bentzen S, Pharoah PD, Barnes DR, et al. Meta-analysis of genome wide association studies identifies genetic markers of late toxicity following radiotherapy for prostate cancer. EBioMedicine 2016;10:150–163. (Available online at: https://doi.org/10.1016/j.ebiom.2016.07.022).

Kerns SL, Ostrer H, Stock R, Li W, Moore J, Pearlman A, et al: Genome-wide association study to identify single nucleotide polymorphisms (SNPs) associated with the development of erectile dysfunction in African-American men after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;78 (5):1292–1300. (Available online at: https://doi.org/S0360-3016(10)00969-7 [pii]10.1016/j.ijrobp.2010.07.036.)

Kimura M, Mouraviev V, Tsivian M, Mayes JM, Satoh T, Polascik TJ: Current salvage methods for recurrent prostate cancer after failure of primary radiotherapy. BJU Int 2010;105 (2):191–201. (Available online at: https://doi.org/10.1111/j.1464-410X.2009.08715.x.)

King CR, Fowler JF. A simple analytic derivation suggests that prostate cancer alpha/beta ratio is low. Int J Radiat Oncol Biol Phys 2001;51:213–214. (Available online at: http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=11516871.)

King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC: 2009. Stereotactic body radiotherapy for localized prostate cancer: Interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys 2009;73(4):1043–1048. (Available online at: https://doi.org/10.1016/j.ijrobp.2008.05.059.)

Kishan AU, Dang A, Katz AL, Mantz CA, Collins SP, Aghdam N, et al: Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. JAMA Network Open 2019a;2(2):e188006. (Available online at: https://doi.org/10.1001/jamanetworkopen.2018.8006.)

Kishan AU, Tyran M, Weng J, Upadhyaya S, Lamb J, Steinberg M, et al: Stereotactic body radiotherapy to the prostate and pelvic lymph nodes: A detailed dosimetric analysis of a phase II prospective trial. Br J Radiol 2019b(March):20181001. (Available online at: https://doi.org/10.1259/bjr.20181001.)

Kishan AU, Katz AJ, Mantz C, Chu F-I, Appelbaum L, Loblaw A, et al: Long-term outcomes of stereotactic body radiotherapy for low- and intermediate-risk prostate adenocarcinoma: A multi-institutional consortium study. J Clin Oncol 2018;36 (6 Suppl):84. (Available online at: https://doi.org/10.1200/JCO.2018.36.6_suppl.84.)

Kjaer SK, Knudsen JB, Sørensen BL, Møller Jensen O, Kjaer K, Sbrensen BL, et al: The Copenhagen Case-Control Study of Bladder Cancer V. Review of the role of urinary-tract infection. Acta Oncologica 2009. (Available online at: https://doi.org/10.3109/02841868909092283.)

Knap MM, Lundbeck F, Overgaard J: Prognostic factors, pattern of recurrence and survival in a Danish bladder cancer cohort treated with radical cystectomy. Acta Oncologica 2003;42(2):160–168. (Available online at: https://doi.org/10.1080/02841860310005039.)

Kollmannsberger C et al: Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. J Clin Oncol 2015;33:51–57.

Kuettel MR, Parda DS, Harter WK, Rodgers JE, Lynch JH: Treatment of female urethral carcinoma in medically inoperable patients using external beam irradiation and high Dose rate intracavitary brachytherapy. J Urol 1997;157(5):1669–1671. (Available online at: https://doi.org/10.1016/S0022-5347(01)64830-4.)

Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, et al: Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys 2004;58:25–33. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14697417.)

Langen KM, Jones DT: Organ motion and its management. Int J Radiat Oncol Biol Phys 50:265–278. (Available online at: https://doi.org/10.1016/S0360-3016(01)01453-5; also at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11316572.)

Langen KM, Pouliot J, Anezinos C, Aubin M, Gottschalk AR, Hsu IC, et al: Evaluation of ultrasound-based prostate localization for image-guided radiotherapy. Int J Radiat Oncol Biol Phys 2003;57:635–644. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14529767.)

Lazar AA, Schulte R, Faddegon B, Blakely EA, Roach M: Clinical trials involving carbon-ion radiation therapy and the path forward. Cancer 2018;124(23):4467–4476. (Available online at: https://doi.org/10.1002/cncr.31662.)

Lee C-Y, Yang K-L, Ko H-L, Huang R-Y, Tsai P-P, Chen M-T, et al: Trimodality bladder-sparing approach without neoadjuvant chemotherapy for node-negative localized muscle-invasive urinary bladder cancer resulted in comparable cystectomy-free survival. Radiat Oncol 2014;9(1):213. (Available online at: https://doi.org/10.1186/1748-717X-9-213.)

Lee WR: The ethics of hypofractionation for prostate cancer. Int J Radiat Oncol Biol Phys 2009;73(4):969–970. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19251081).

Lee WR, Bae K, Lawton C, Gillin M, Morton G, Firat S, et al: Late toxicity and biochemical recurrence after external-beam radiotherapy combined with permanent-source prostate Brachytherapy: Analysis of Radiation Therapy Oncology Group Study 0019. Cancer 2007;109(8):1506–1512. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17340591.)

Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al: Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 2016;34(20):2325–2332. (Available online at: https://doi.org/10.1200/JCO.2016.67.0448.)

Leman ES, Gonzalgo ML: Prognostic features and markers for testicular cancer management. Indian J Urol 2010;26(1):76–81. (Available online at: https://doi.org/10.4103/0970-1591.60450.)

Lennernas B, Majumder K, Damber JE, Albertsson P, Holmberg E, Brandberg Y, et al: Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes. Acta Oncol 2015;54(6):875–881. (Available online at: https://doi.org/10.3109/0284186X.2014.974827.)

Libby B, Chao D, Schneider BF: Non-surgical treatment of primary female urethral cancer. Rare Tumors 2010;2(3):158–160; see also

Mehus B, Elliott SP: Urinary adverse effects of pelvic radiotherapy. Transl Androl Urol 2014;3(2):186–195. (Available online at: https://doi.org/10.3978/j.issn.2223-4683.2014.04.01.)

Ludwig MS, Kuban DA, Strom SS, Du XL, Lopez DS, Yamal JM: The role of androgen deprivation therapy on biochemical failure and distant metastasis in intermediate-risk prostate cancer: Effects of radiation dose escalation. BMC Cancer 2015;15(1):190. (Available online at: https://doi.org/10.1186/s12885-015-1180-6.)

Lukka H, Hayter C, Julian JA, Warde P, Morris WJ, Gospodarowicz M, et al: Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol 2005;23(25):6132–6138. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16135479.)

Maarouf AM, Khalil S, Salem EA, El Adl M, Nawar N, Zaiton F: Bladder preservation multimodality therapy as an alternative to radical cystectomy for treatment of muscle invasive bladder cancer. BJU Int 2011;107(10):1605–1610. (Available online at: https://doi.org/10.1111/j.1464-410X.2010.09564.x.)

Maase H von der, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23(21):4602–4608. (Available online at: https://doi.org/10.1200/JCO.2005.07.757.)

Maddineni SB, Sangar VK, Hendry JH, Margison GP, Clarke NW: Differential radiosensitisation by ZD1839 (Iressa), a highly selective epidermal growth factor receptor tyrosine kinase inhibitor in two related bladder cancer cell lines. Br J Cancer 2005;92(1):125–130. (Available online at: https://doi.org/10.1038/sj.bjc.6602299.)

Magnuson WJ, Bradley K, Shaves M: Successful management of female urethral carcinoma with radiation therapy and concurrent chemotherapy. Gynecol Oncol Case Rep 2011;2(1):1–3. (Available online at: https://doi.org/10.1016/j.gynor.2011.10.006.)

Mak RH et al: Long-Term Outcomes in Patients With Muscle-Invasive Bladder Cancer After Selective Bladder-Preserving Combined-Modality Therapy: A Pooled Analysis of Radiation Therapy Oncology Group Protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol 2014;32:3801–3809.

Martin JM, Panzarella T, Zwahlen DR, Chung P, Warde P: Evidence-based guidelines for following stage 1 seminoma. Cancer 2007;109(11):2248–2256. (Available online at: https://doi.org/10.1002/cncr.22674.)

Martinez A, Orton C, Mould R: Brachytherapy HDR and LDR. In: Bertermann H, Brix F (eds): Ultrasound Guided Interstitial High Dose Brachytherapy with Iridium-192: Technique and Preliminary Results in Locally Confined Prostate Cancer. Nucletron, Columbia, MD, 1990.

Mazeron JJ, Langlois D, Lobo PA, et al: Interstitial radiation therapy for carcinoma of the penis using iridium 192 wires: The Henri Mondor experience (1970–1979). Int J Radiat Oncol Biol Phys 1984;10:1891–1895.

McCammon R, Rusthoven KE, Kavanagh B, Newell, Newman F, Raben D: Toxicity assessment of pelvic intensity-modulated radiotherapy with hypofractionated simultaneous integrated boost to prostate for intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2009. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19362783.)

McMahon SJ, Prise KM: Mechanistic modelling of radiation responses. Cancers 2019;11(2):205. (Available online at: https://doi.org/10.3390/cancers11020205.)

Melotek JM, Liao C, Liauw SL: Quality of life after post-prostatectomy intensity modulated radiation therapy: Pelvic nodal irradiation is not associated with worse bladder, bowel, or sexual outcomes. PLoS ONE 2015;10(10):1–11. (Available online at: https://doi.org/10.1371/journal.pone.0141639.)

Memmelaar J: Total prostatovesiculectomy; retropubic approach. J Urol 1949;62(3):340–348. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18148289.)

Michalski J, Winter K, Roach M, Markoe A, Sandler HM, Ryu J, et al: Clinical outcome of patients treated with 3D conformal radiation therapy (3D-CRT) for prostate cancer on RTOG 9406. Int J Radiat Oncol Biol Phys 2012;83(3):e363–e370. (Availabe online at: https://doi.org/10.1016/j.ijrobp.2011.12.070.)

Millender LE, Aubin M, Pouliot J, Shinohara K, Roach M 3rd. Daily electronic portal imaging for morbidly obese men undergoing radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2004;59:6–10. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15093893.)

Miller LS: Bladder cancer. superiority of preoperative irradiation and cystectomy in clinical stages B2 and C. Cancer 1977;39(S2):973–980. (Available online at: https://doi.org/10.1002/1097-0142(197702)39:2+<973::AID-CNCR2820390737>3.0.CO;2-O.)

Mitin T et al: Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. Lancet Oncol 2013;14:863–872.

Mizoguchi N, Tsuji H, Toyama S, Kamada T, Tsujii H, Nakayama Y, et al: Carbon-ion radiotherapy for locally advanced primary or postoperative recurrent epithelial carcinoma of the lacrimal gland. Radiother Oncol 2015;114(3):373–377. (Available online at: https://doi.org/10.1016/j.radonc.2015.01.009.)

Mohammed N, Kestin L, Ghilezan M, Krauss D, Vicini F, Brabbins D, et al: Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. Int J Radiat Oncol Biol Phys 2010. (Available online at: https://doi.org/S0360-3016(10)03427-9 [pii]10.1016/j.ijrobp.2010.10.009).

Mohler J, Bahnson RR, Boston B, Busby JE, D'Amico A, Eastham JA, et al: n.d. NCCN clinical practice guidelines in oncology: Prostate cancer. J Natl Compr Canc Netw 2010;8(2):162–200. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20141676.)

Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al: Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline. J Clin Oncol 2018;36(34):3411–3430. (Available online at: https://doi.org/10.1200/JCO.18.01097.)

Morgan SC, Rumble RB, Sandler H: Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline summary. J Oncol Pract 2019;15(1):50–54. (Available online at: https://doi.org/10.1200/JOP.18.00616.)

Morris WJ, Pickles T, Keyes M, McKenzie M, Spadinger I: Pride or prejudice: Does Phoenix flatter radiation therapy? Brachytherapy 2014;13(3):299–303. (Available online at: https://doi.org/10.1016/j.brachy.2013.06.006.)

Mortensen MS et al: A Nationwide Cohort Study of Stage I Seminoma Patients Followed on a Surveillance Program. Eur Urol 2014;66:1172–1178.

Moul JW, Kibel AS, Roach M 3rd, Dreicer R: Indications and practice with androgen deprivation therapy. Urology 2011;78(5 Suppl):S478–S481. (Available online at: https://doi.org/10.1016/j.urology.2011.04.025.)

Muñoz JJ, Drigo SA, Barros-Filho MC, Marchi FA, Scapulatempo-Neto C, Pessoa GS, et al: Down-regulation of SLC8A1 as a putative apoptosis evasion mechanism by modulation of calcium levels in penile carcinoma. J Urol 2015;194(1):245–251. (Available online at: https://doi.org/10.1016/j.juro.2014.11.097.)

Muro X Garcia del, Condom E, Vigués F, Castellsagué X, Figueras A, Muñoz J, et al: P53 and P21 expression levels predict organ preservation and survival in invasive bladder carcinoma treated with a combined-modality approach. Cancer 2004;100(9):1859–1867. (Available online at: https://doi.org/10.1002/cncr.20200.)

Nalesnik JG, Sabanegh ES, Eng TY, Buchholz TA: Fertility in men after treatment for stage 1 and 2A seminoma. Am J Clin Oncol 2004;27(6):584–588. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/15577436.)

Nanda A, Chen MH, Moran BJ, Braccioforte MH, Dosoretz D, Salenius S, et al: Neoadjuvant hormonal therapy use and the risk of death in men with prostate cancer treated with brachytherapy who have no or at least a single risk factor for coronary artery disease. Eur Urol 2014;65(1):177–185. (Available online at: https://doi.org/10.1016/j.eururo.2012.08.070.)

Nguyen PL, Chen RC, Clark JA, Cormack RA, Loffredo M, McMahon E, et al: Patient-reported quality of life after salvage brachytherapy for radio-recurrent prostate cancer: A prospective phase II study. Brachytherapy 2009;8(4):345–352. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19428311.)

Nguyen QN, Shiu AS, Rhines LD, Wang H, Allen PK, Wang XS, et al: Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76(4):1185–1192. (Available online at: https://doi.org/10.1016/J.IJROBP.2009.03.062.)

Niazi TM, Souhami L, Sultanem K, Duclos M, Shenouda G, Freeman C: Long-term results of para-aortic irradiation for patients with stage I seminoma of the testis. Int J Radiat Oncol Biol Phys 2005;61(3):741–744. (Available online at: https://doi.org/10.1016/j.ijrobp.2004.06.247.)

Nichols RC, Sweetser MG, Mahmood SK, Malamud FC, Dunn NP, Adams JP, et al: Radiation therapy and concomitant paclitaxel/carboplatin chemotherapy for muscle invasive transitional cell carcinoma of the bladder: A well-tolerated combination. Int J Cancer 2000;90(5):281–286. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11091352.)

Nicholson S, Tsang D, Summerton D: Aggressive combined-modality therapy for squamous cell carcinoma of the female urethra. Nat Clin Pract Urol 2008;5(10):574–577. (Available online at: https://doi.org/10.1038/ncpuro1211.)

Niewald M, Waziri A, Walter K, Nestle U, Schnabel K, Humke U: Low-dose radiotherapy for stage I seminoma: Early results. Radiother Oncol 1995;37(2):164–166. (Available online at: https://doi.org/10.1016/0167-8140(95)01631-P.)

Nikolaev A, Benda R: Palliative radiation therapy for symptomatic control of inoperable renal cell carcinoma. Urol Case Rep 2016;4:51–52. (Available online at: https://doi.org/10.1016/J.EUCR.2015.09.006.)

Ning S, Trisler k, Wessels BW, Knox SJ: Radiobiologic studies of radioimmunotherapy and external beam radiotherapy in vitro and in vivo in human renal cell carcinoma xenografts. Cancer 1997;80(S12):2519–2528. (Available online at: https://doi.org/10.1002/(SICI)1097-0142(19971215)80:12+<2519::AID-CNCR26>3.0.CO;2-E.)

Nudell DM, Grossfeld GD, Weinberg VK, Roach M 3rd, Carroll PR: Radiotherapy after radical prostatectomy: Treatment outcomes and failure patterns. Urology 1999;54:1049–1057. (Available online at: http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=10604707.)

Oh JH, Kerns S, Ostrer H, Powell SN, Rosenstein B, Deasy JO: Computational methods using genome-wide association studies to predict radiotherapy complications and to identify correlative molecular processes. Sci Rep 2017;7:43381. (Available online at: https://doi.org/10.1038/srep43381.)

Oliver RTD, Mead GM, Rustin GJS, Joffe JK, Aass N, Coleman, RG, et al: Randomized trial of carboplatin versus radiotherapy for stage I seminoma: Mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 2011;29(8):957–962. (Available online at: https://doi.org/10.1200/JCO.2009.26.4655.)

Oliver RTD, Mason MD, Mead GM, von der Maase H, Rustin GJS, Joffe JK, et al: Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: A randomised trial. Lancet (London) 2005;366(9482):293–300. (Available onine at: https://doi.org/10.1016/S0140-6736(05)66984-X.)

Ornellas AA, Seixas AL, Marota A, et al: Surgical treatment of invasive squamous cell carcinoma of the penis: Retrospective analysis of 350 cases. J Urol 1994;151:1244–1249.

Paly JJ, Efstathiou JA, Hedgire SS, Chung PWM, O'Malley M, Shah A, et al: Lymph node metastases mapping patterns of nodal metastases in seminoma: Rethinking radiotherapy fields. Radiother Oncol 2013;106:64–68. (Available online at: https://doi.org/10.1016/j.radonc.2012.12.002.)

Parashar B, Patro KC, Smith M, Arora S, Nori D, Wernicke AG: Role of radiation therapy for renal tumors. Semin Intervent Radiol 2014;31(1):86–90. (Available online at: https://doi.org/10.1055/s-0033-1363847.)

Parisi S, Troiano M, Corsa P, Raguso A, Cossa S, Piazzolla EE, et al: Role of external radiation therapy in urinary cancers. Ann Oncol 2007;18:157–161. (Available online at: https://doi.org/10.1093/annonc/mdm247.)

Parker C, Milosevic M, Panzarella T, Banerjee D, Jewett M, Catton C, et al: The prognostic significance of the tumour infiltrating lymphocyte count in stage I testicular seminoma managed by surveillance. Eur J Cancer 2002;38(15):2014–2019. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/12376206.)

Patterson H, Norman AR, Mitra SS, Nicholls J, Fisher C, Dearnaley DP, et al: Combination carboplatin and radiotherapy in the management of stage II testicular seminoma: Comparison with radiotherapy treatment alone. Radiother Oncol 2001;59(1):5–11. (Available online at: https://doi.org/10.1016/S0167-8140(00)00240-1.)

Peach MS, Trifiletti DM, Libby B: Systematic review of focal prostate brachytherapy and the future implementation of image-guided prostate HDR brachytherapy using MR-ultrasound fusion. Prostate Cancer 2016:4754031 (Available online at: https://doi.org/10.1155/2016/4754031.)

Peeters A, Grutters JP, Pijls-Johannesma M, Reimoser S, De Ruysscher D, Severens JL, et al: How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiother Oncol 2010;95(1):45–53. (Available online at: https://doi.org/10.1016/j.radonc.2009.12.002.)

Pellizzon AC, Nadalin W, Salvajoli JV, Fogaroli RC, Novaes PE, Maia MA, et al: Results of high dose rate afterloading brachytherapy boost to conventional external beam radiation therapy for initial and locally advanced prostate cancer. Radiother Oncol 2003;66(2):167–172. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12648788.)

Petrovich Z, Jozsef G, Brady LW: Radiotherapy for carcinoma of the bladder: A review. Am J Clin Oncol 2001;24(1):1–9. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11232941.)

Pinkawa M, Fischedick K, Asadpour B, Gagel B, Piroth MD, Holy R, et al: Health-related quality of life after adjuvant and salvage postoperative radiotherapy for prostate cancer - a prospective analysis. Radiother Oncol 2008;88(1):135–139. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18022263.)

Pinkawa M, Piroth MD, Holy R, Fischedick K, Klotz J, Szekely-Orban D, et al: Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: A matched-pair comparison. Int J Radiat Oncol Biol Phys 2010;81(1):23–28. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20832182.)

Pisansky TM, Hunt D, Gomella LG, Amin MB, Balogh AG, Chinn DM, et al: Duration of androgen suppression before radiotherapy for localized prostate cancer: Radiation Therapy Oncology Group Randomized Clinical Trial 9910. J Clin Oncol 2015;33(4):332–339. (Available online at: https://doi.org/10.1200/JCO.2014.58.0662.)

Pollack A, Karrison TG, Balogh AG, Low D, Bruner DW, Wefel JS, et al: LBA5 short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: The NRG Oncology/RTOG 0534 SPPORT Trial LBA6 plasma circulating tumor HPV DNA for the surveillance of cancer recurrence in HPV-associated oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2018;102. (Available online at: https://doi.org/10.1016/j.ijrobp.2018.08.052.)

Pos FJ, Koedooder K, Hulshof MCCM, van Tienhoven G, González DG: Influence of bladder and rectal volume on spatial variability of a bladder tumor during radical radiotherapy. Int J Radiat Oncol Biol Phys 2003;55(3):835–841 (Available online at: https://doi.org/10.1016/S0360-3016(02)04158-5.)

Pouliot J, Aubin M, Langen KM, Liu YM, Pickett B, Shinohara K et al: (Non)-migration of radiopaque markers used for on-line localization of the prostate with an electronic portal imaging device. Int J Radiat Oncol Biol Phys 2003;56:862–866. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12788196.)

Pozzo LF Da, Cozzarini C, Briganti A, Suardi N, Salonia A, Bertini R, et al: Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: The positive impact of adjuvant radiotherapy. Eur Urol 2009. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19211184.)

Prestidge WK, Sanda MG, Amin MB, Bice Jr WS, Michalski JM, Ibbott GS, et al: Initial report of NRG Oncology/RTOG 0232: A phase III study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for selected patients with intermediate risk prostatic carcinoma. Int J Radiat Biol 2016:S4.

Prosnitz RG, Schneider L, Manola J, Rocha S, Loffredo M, Lopes L, et al: Tamsulosin palliates radiation-induced urethritis in patients with prostate cancer: Results of a pilot study. Int J Radiat Oncol Biol Phys 1999;45(3):563–566. (Avaiable online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10524406.)

Reiner Walsh PCWB: An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. J Urol 1979;121:198.

Reiter WJ, Brodowicz T, Alavi S, Zielinski CC, Kozak W, Maier U, et al: Twelve-year experience with two courses of adjuvant single-agent carboplatin therapy for clinical stage I seminoma. J Clin Oncol 2001;19(1):101–104. (Available onlline at: https://doi.org/10.1200/JCO.2001.19.1.101.)

Ritter M, Forman J, Kupelian P, Lawton C, Petereit D: Hypofractionation for prostate cancer. Cancer J 2009;15(1):1–6. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19197165.)

Roach M 3rd: Re: Morbidity and mortality of locally advanced prostate cancer: A population based analysis comparing radical prostatectomy versus external beam radiation. Eur Urol 2018;73(4):638–639. (Available online at: https://doi.org/10.1016/j.eururo.2017.12.009.)

Roach M 3rd, Moughan J, Lawton CAF, Dicker AP, Zeitzer KL, Gore EM, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): Long-term results of a randomised, phase 3 trial. Lancet Oncol 2018;19(11):1504–1515. (Available online at: https://doi.org/10.1016/S1470-2045(18)30528-X.)

Roach M 3rd, Ceron Lizarraga TL, Lazar AA: Radical prostatectomy versus radiation and androgen deprivation therapy for clinically localized prostate cancer: How good is the evidence? Int J Radiat Oncol Biol Phys 2015;93(5):1064–1070. (Available online at: https://doi.org/10.1016/j.ijrobp.2015.08.005.)

Roach M 3rd, Thomas K: Overview of randomized controlled treatment trials for clinically localized prostate cancer: Implications for active surveillance and the United States preventative task force report on screening? J Natl Cancer Inst Monogr 2012(45):221–229. (Available online at: https://doi.org/10.1093/jncimonographs/lgs039.)

Roach M 3rd, Yan Y, Lawton CA, Hsu I-CJ, Lustig RA, Jones CU, et al: Radiation Therapy Oncology Group (RTOG) 9413: Randomized trial comparing whole pelvic radiotherapy (WPRT) to prostate only (PORT) and neoadjuvant hormone therapy (NHT) to adjuvant hormone therapy (AHT). In: Proceedings of 2012 ASCO Genitourinary Symposium. Vol. 30. San Francisco, 2012.

Roach M 3rd, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB: Radiation dose volume effects and the penile bulb. Int J Radiat Oncol Biol Phys 2010.

Roach M 3rd, Weinberg V, Sandler H, Thompson I: 2007. Staging for prostate cancer: Time to incorporate pretreatment prostate-specific antigen and Gleason score? Cancer 2007;109(2):213–220. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17167758.)

Roach M 3rd, Hanks MG, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, et al: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006a;65(4):965–74. https://doi.org/10.1016/j.ijrobp.2006.04.029.

Roach M 3rd, Weinberg V, Nash M, Sandler HM, McLaughlin PW, Kattan MW: Defining high risk prostate cancer with risk groups and nomograms: Implications for designing clinical trials. J Urol 2006b;176(6 Pt 2):S16–S20. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17084158.)

Roach M 3rd, Weinberg V, McLaughlin PW, Grossfeld G, Sandler HM. Serum prostate-specific antigen and survival after external beam radiotherapy for carcinoma of the prostate. Urology 2003;61:730–735. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12670556.)

Roach M, Lu J, Pilepich MV, Asbell SO, Mohiuddin M, Terry R, Grignon D: Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group Clinical Trials. Int J Radiat Oncol Biol Phys 2000;47(3):609–615. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10837943.)

Robinson R, Marconi L, MacPepple E, Hakenberg W, Watkin N, Yuan Y, et al: Risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy in node-positive penile cancer: A systematic review by the European Association of Urology Penile Cancer Guidelines Panel. Eur Urol 2018;74(1):76–83. (Available online at: https://doi.org/10.1016/j.eururo.2018.04.003.)

Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, et al: 2017. ASCENDE-RT: An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98(2):286–295. (Available online at: https://doi.org/10.1016/j.ijrobp.2017.01.008.)

Rödel C, Grabenbauer GC, Kühn R, Papadopoulos T, Dunst J, Meyer M, et al: Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. J Clin Oncol 2002;20(14):3061–3071. (Available online at: https://doi.org/10.1200/JCO.2002.11.027.)

Rodrigues G, Bae K, Roach M 3rd, Lawton C, Donnelly B, Grignon D, et al: Impact of ultrahigh baseline PSA levels on biochemical and clinical outcomes in two Radiation Therapy Oncology Group prostate clinical trials. Int J Radiat Oncol Biol Phys 2011;80(2):445–452. (Available online at: https://doi.org/10.1016/j.ijrobp.2010.02.034.)

Rogers Grossfeld GD, Roach M 3rd, Shinohara K., Presti JC, Carroll PRR: Radiation therapy for the management of biopsy-proven, local recurrence following radical prostatectomy. J Urol 1998;160:1748–1753.

Ross AE, Feng FY, Ghadessi M, Erho N, Crisan A, Buerki C, et al: A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate Cancer Prostatic Dis 2014;17(1):64–69. (Available online at: https://doi.org/10.1038/pcan.2013.49.)

Rost A, Brosig W: Preoperative irradiation of renal cell carcinoma. Urology 1977;10(5):414–417. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/411207.)

Rouscoff Y, Falk A, Durand M, Gal J, Chand M-E, Gautier M, et al: High-dose rate brachytherapy in localized penile cancer: Short-term clinical outcome analysis. Radiat Oncol 2014;9(1):142. (Available online at: https://doi.org/10.1186/1748-717X-9-142.)

Rowland RG: Stage II testicular seminoma: Patterns of recurrence and outcome of treatment. Urol Oncol 2005;23(2):140–141. (Available online at: https://doi.org/10.1016/J.UROLONC.2005.01.014.)

Royce TJ, Feldman AS, Mossanen M, Yang JC, Shipley WU, Pandharipande PV, et al: Comparative effectiveness of bladder-preserving tri-modality therapy versus radical cystectomy for muscle-invasive bladder cancer. *Clinical Genitourinary Cancer* 2019;17 (1): 23–31.e3. https://doi.org/10.1016/j.clgc.2018.09.023.

Rozan R, Albuisson E, Giraud B, Donnarieix D, Delannes M, Pigneux J, et al: Interstitial brachytherapy for penile carcinoma: A multicentric survey (259 patients). Radiother Oncol 1995;36(2):83–93. (Available online at: https://doi.org/10.1016/0167-8140(95)01574-Z.)

Sahgal A, Roach M 3rd: 2007. Permanent prostate seed brachytherapy: A current perspective on the evolution of the technique and its application. Natl Clin Pract Urol 2007;4(12):658–670. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18059346.)

Salami SS, Montgomery JS: Surveillance strategies in the management of penile cancer. *Transl Androl Urol* 2017;6(5):868–873. (Available online at: https://doi.org/10.21037/tau.2017.06.04.)

Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, Lin X, et al: Quality of life and satisfaction with outcome among prostate-cancer survivors. New Engl J Med 2008;358 (12):1250–1261. (Available online at: https://doi.org/10.1056/NEJMoa074311.)

Sangar VK, McBain CA, Lyons J, Ramani VAC, Logue JP, Wylie JP, et al: Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. Int J Radiat Oncol Biol Phys 2005;61(2):420–425. (Available online at: https://doi.org/10.1016/j.ijrobp.2004.05.074.)

Sarin R, Andrew R. Norman AR, Steel GG, Horwich A: Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys 1997;38(4):713–722. (Available online at: https://doi.org/10.1016/S0360-3016(97)00068-0.)

Sauer R et al: Efficacy of radiochemotherapy with platin derivatives compared to radiotherapy alone in organ-sparing treatment of bladder cancer. Int J Radiat Oncol Biol Phys 1998;40:121–127.

Schiffner DC, Gottschalk AR, Lometti M, Aubin M, Pouliot J, Speight J, et al: Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy. Int J Radiat Oncol Biol Phys 2007;67(2):610–619. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17236978.)

Shariat SF, Karakiewicz PI, Palapattu GS, Lotan Y, Rogers CG, Amiel GE, et al: Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: A contemporary series from the Bladder Cancer Research Consortium. J Urol 2006;176(6):2414–2422. (Available online at: https://doi.org/10.1016/j.juro.2006.08.004.)

Sharma DN, Gandhi AK, Bhatla N, Kumar S, Rath GK: High-dose-rate interstitial brachytherapy for female peri-urethral cancer. J Contemp Brachyther 2016;1:41–47. (Available online at: https://doi.org/10.5114/jcb.2016.57461.)

Sheehan JP, Sun M-H, Kondziolka D, Flickinger J, Dade Lunsford L: Radiosurgery in patients with renal cell carcinoma metastasis to the brain: Long-term outcomes and prognostic factors influencing survival and local tumor control. J Neurosurg 2003;98(2):342–349. (Available online at: https://doi.org/10.3171/jns.2003.98.2.0342.)

Shelley M, Barber J, Wilt TJ, Mason M: Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database

Syst Rev 2001;(1):CD002079. (Available online at: https://doi.org/10.1002/14651858.CD002079.)

Shimizu S, Shirato H, Kitamura K, Shinohara N, Harabayashi T, Tsukamoto T, et al: Use of an implanted marker and real-time tracking of the marker for the positioning of prostate and bladder cancers. Int J Radiat Oncol Biol Phys 2000;48(5):1591–1597. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11121666.)

Shinohara K, Roach M 3rd: Technique for implantation of fiducial markers in the prostate. Urology 2008;71(2):196–200. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18308082.)

Shipley WU, Verhey LJ, Munzenrider JE, Suit HD, Urie MM, McManus PL, et al: Advanced prostate cancer: The results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. Int J Radiat Oncol Biol Phys 1995;32(1):3–12. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7721636.)

Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, et al: Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with Selective bladder preservation by combined radiation therapy and chemotherapy: Initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 1998;16(11):3576–3583. (Available online at: https://doi.org/10.1200/JCO.1998.16.11.3576.)

Shipley WU, Kaufman DS, Tester WJ, Pilepich MV, Sandler HM: Overview of bladder cancer trials in the Radiation Therapy Oncology Group. Cancer 2003;97(S8):2115–2119. (Available online at: https://doi.org/10.1002/cncr.11282.)

Shipley WU et al: The success of radiation therapy in controlling prostatic cancer within the treated field. Prog Clin Biol Res 1987;243B:199–212.

Simone CB, Kramer K, O'Meara WP, Bekelman JE, Belard A, McDonough J, et al: Predicted rates of secondary malignancies from proton versus photon radiation therapy for stage I seminoma. Int J Radiat Oncol Biol Phys 2012;82(1):242–249. (Available online at: https://doi.org/10.1016/J.IJROBP.2010.11.021.)

Simpson WG, Klaassen Z, Jen RP, Hughes WM, Neal DE, Terris MK: Analysis of suicide risk in patients with penile cancer and review of the literature. Clin Genitour Cancer 2018;16(2):e257–e261. (Available online at: https://doi.org/10.1016/j.clgc.2017.09.011.)

Siracusano S, D'Elia C, Cerruto MA, Saleh O, Serni S, Gacci M, et al: Quality of life in patients with bladder cancer undergoing ileal conduit: A comparison of women versus men. In Vivo 2018;32(1):139–143. (Available online at: https://doi.org/10.21873/invivo.11216.)

Smith BW, Joseph JR, Saadeh YS, La Marca F, Szerlip NJ, Schermerhorn TC, et al: Radiosurgery for treatment of renal cell metastases to spine: A systematic review of the literature. World Neurosurg 2018;109:e502–e509. (Available online at: https://doi.org/10.1016/J.WNEU.2017.10.011.)

Smith JA, Labasky RF, Cockett AT, Fracchia JA, Montie JE, Rowland RG: Bladder Cancer Clinical Guidelines Panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. *J Urol* 1999;162(5):1697–1701. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/10524909.)

Soria J-C, Fizazi K, Piron D, Kramar A, Gerbaulet A, Haie-Meder C, et al: Squamous cell carcinoma of the penis: Multivariate analysis of prognostic factors and natural history in a monocentric study with a conservative policy. *Ann Oncol* 1997;8(11):1089–1098. (Available online at: https://doi.org/10.1023/A:1008248319036.)

Spera JA, Whittington R, Littman P, Solin LJ, Wein AJ: A comparison of preoperative radiotherapy regimens for bladder carcinoma. 1988, (n.d.) (Available online at: https://onlinelibrary.wiley.com/doi/pdf/10.1002/1097-0142(19880115)61:2%3C255::AID-CNCR2820610210%3E3.0.CO;2-X; accessed 4/1/19.)

Spiotto MT, Hancock SL, King CR: Radiotherapy after prostatectomy: Improved biochemical relapse-free survival with whole pelvic compared with prostate bed only for high-risk patients. Int J Radiat Oncol Biol Phys 2007;69(1):54–61. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17459606.)

Spratt DE, Dess RT, Zumsteg ZS, Lin DW, Tran PT, Morgan TM, et al: A systematic review and framework for the use of hormone therapy with salvage radiation therapy for recurrent prostate cancer. Eur Urol 2018a;73(2):156–165. (Available online at: https://doi.org/10.1016/j.eururo.2017.06.027.)

Spratt DE, Zhang J, Santiago-Jiménez M, Dess RT, Davis JW, Den RB, et al: Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. J Clin Oncol 2018b;36(6):581–590. (Available online at: https://doi.org/10.1200/JCO.2017.74.2940.)

Stein JP, Skinner DG: Results with radical cystectomy for treating bladder cancer: A "reference standard" for high-grade, invasive bladder cancer. BJU Int 2003;92(1):12–17. (Available online at: https://doi.org/10.1046/j.1464-410X.2003.04274.x.)

Stein JP, Lieskovsky G, Cote R, Groshen S, Feng A-C, Boyd S, et al: Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol 2001;19(3):666–675. (Available online at: https://doi.org/10.1200/JCO.2001.19.3.666.)

Steiner H, Scheiber K, Berger AP, Rein P, Hobisch A, Aufderklamm J, et al: Retrospective multicentre study of carboplatin monotherapy for clinical stage I seminoma. BJU Int 2011;107(7):1074–1079. (Available online at: https://doi.org/10.1111/j.1464-410X.2010.09658.x.)

Stone NN, Potters L, Davis BJ, Ciezki JP, Zelefsky MJ, Roach M 3rd, et al: 2009. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7–10 prostate cancer treated with permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2009;73(2):341–346. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18597953.)

Swartz MA, Porter MP, Lin DW, Weiss NS: Incidence of primary urethral carcinoma in the United States. Urology 2006;68(6):1164–1168. (Available online at: https://doi.org/10.1016/J.UROLOGY.2006.08.1057.)

Tang N, Bueno M, Meylan S, Incerti S, Tran HN, Vaurijoux A, et al: Influence of chromatin compaction on simulated early radiation-induced DNA damage using Geant4-DNA. Med Phys 2019;46(3):1501–1511. (Available online at: https://doi.org/10.1002/mp.13405.)

Teh B, Bloch C, Galli-Guevara M, Doh L, Richardson S, Chiang S, et al: The treatment of primary and metastatic renal cell carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT). Biomed Imaging Intervent J 2007;3(1):e6. (Available online at: https://doi.org/10.2349/biij.3.1.e6.)

Tendulkar RD, Agrawal S, Gao T, Efstathiou JA, Pialsansky TM, Michalski JM, et al: 2016. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 2016;34(30):3648–3654. (Available online at: https://doi.org/10.1200/JCO.2016.67.9647.)

Tester W, Porter A, Asbell S, Coughlin C, Heaney J, Krall J, et al: Combined modality program with possible organ preservation for invasive bladder carcinoma: Results of RTOG Protocol 85-12. *Int J Radiat Oncol Biol Phys* 1993;25(5):783–790. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/8478228.)

Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term followup of a randomized clinical trial. *J Urol* 2009;181(3):956–962. (Available online at: https://doi.org/10.1016/j.juro.2008.11.032.)

Travis LB, Fosså SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al: Second cancers among 40 576 testicular cancer patients: Focus on long-term survivors. J Natl Cancer Inst 2005;97(18):1354–1365. (Available online at: https://doi.org/10.1093/jnci/dji278.)

Valicenti RK, Gomella LG, Ismail M, Strup SE, Mulholland SG, Dicker AP, et al: The efficacy of early adjuvant radiation therapy for PT3N0 prostate cancer: A matched-pair analysis. Int J Radiat Oncol Biol Phys 1999;45:53–58.

Viswanathan AN, Beriwal S, De Los Santos JF, Demanes DJ, Gaffney D, Hansen J, Jones E, et al: American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy. Brachytherapy 11(1):47–52. (Available online at: https://doi.org/10.1016/j.brachy.2011.07.002.)

Wallis CJ, Saskin R, Choo R, Herschorn S, Kodama T, Satkunasivam R, et al: Surgery versus radiotherapy for clinically-localized prostate cancer: A systematic review and meta-analysis. Eur Urol 2015;70(1):21–30. (Available online at: https://doi.org/10.1016/j.eururo.2015.11.010.)

Warde PR, Chung P, Sturgeon J, Panzarella T, Giuliani M, Tew-George B, et al: Should surveillance be considered the standard of care in stage I seminoma? J Clin Oncol 2005;23(16 Suppl):4520. (Available online at: https://doi.org/10.1200/jco.2005.23.16_suppl.4520.)

Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al: Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. Lancet (London) 2011;378(9809):2104–2111. (Available online at: https://doi.org/10.1016/S0140-6736(11)61095-7.)

Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, et al: Prognostic factors for relapse in stage I seminoma managed by surveillance: A pooled analysis. J Clin Oncol 2002;20(22):4448–4452. (Available online at: https://doi.org/10.1200/JCO.2002.01.038.)

Weiss LA, Pan L, Abney M, Ober C: The sex-specific genetic architecture of quantitative traits in humans. Nat Genet 2006;38(2):218–222. (Available online at: https://doi.org/10.1038/ng1726.)

Werf-Messing BH van der, Friedell GH, Menon RS, Hop WC, Wassif SB: Carcinoma of the urinary bladder category T3 NX MO treated by preoperative irradiation followed by simple cystectomy. Progress Clin Biol Res 1988;260:453–460. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/3129735.)

Werf-Messing BHP van der, Friedell GH, Menon RS, Hop WCJ, Wassif SB: Carcinoma of the urinary bladder T3NxMo treated by preoperative irradiation followed by simple cystectomy. *Int J Radiat Oncol Biol Phys* 1982;8(11):1849–1855. (Available online at: https://doi.org/10.1016/0360-3016(82)90441-2.)

Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, et al: Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96–02/AUO AP 09/95 Trial. Eur Urol 2014;66(2):243–250. (Available online at: https://doi.org/10.1016/j.eururo.2014.03.011.)

Williams S, Buyyounouski M, Kestin L, Duchesne G, Pickles T: Predictors of androgen deprivation therapy efficacy combined with prostatic irradiation: The central role of tumor stage and radiation dose. Int J Radiat Oncol Biol Phys 2011;79(3):724–731. (Available online at: https://doi.org/10.1016/j.ijrobp.2009.11.044.)

Willoughby T, Kupelian P, Pouliot J, Shinohara K, Aubin M, Roach M 3rd, et al: Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. Int J Radiat Biol Phys 2006;65:528–534.

Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL: Systematic review: Comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med 2008;148(6):435–448. (Available online at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18252677.)

Wolf H, Melsen F, Pedersen SE, Nielsen KT: Natural history of carcinoma in situ of the urinary bladder. Scand J Urol Nephrol Suppl 1994;157:147–151. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/7939446.)

Yu JB, Soulos PR, Herrin J, Cramer LD, Potosky AL, Roberts KB, et al: Proton versus intensity-modulated radiotherapy for prostate cancer: Patterns of care and early toxicity. J Natl Cancer Inst 2013;105(1):25–32. (Available online at: https://doi.org/10.1093/jnci/djs463.)

Zaffuto E, Gandaglia G, Fossati N, Dell'Oglio P, Moschini M, Cucchiara V, et al: Early postoperative radiotherapy is associated with worse functional outcomes in patients with prostate cancer. J Urol 2017;197(3 Pt 1):669–675. (Available online at: https://doi.org/10.1016/j.juro.2016.09.079.)

Zapatero A, Guerrero A, Maldonado X, Alvarez A, Gonzalez San Segundo C, Rodríguez MAC, et al High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): A randomised, controlled, phase 3 trial. Lancet Oncol 2015;16(3):320–327. (Available at: https://doi.org/10.1016/S1470-2045(15)70045-8.)

Zelefsky MJ, Gomez DR, Polkinghorn WR, Pei X, Kollmeier M: Biochemical response to androgen deprivation therapy before external beam radiation therapy predicts long-Term prostate cancer survival outcomes. Int J Radiat Oncol Biol Phys 2013;86(3):529–533. (Available online at: https://doi.org/10.1016/j.ijrobp.2013.02.004.)

Zhao SG, Chang SL, Erho N, Yu M, Lehrer J, Alshalalfa M, et al: Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. JAMA Oncol 2017;3(12):1663–1672. (Available online at: https://doi.org/10.1001/jamaoncol.2017.0751.)

Zhu H, Wang Z, Xu Q, Zhang Y, Zhai Y, Bai J, et al: Inhibition of STAT1 sensitizes renal cell carcinoma cells to radiotherapy and chemotherapy. Cancer Biol Ther 2012;13(6):401–407. (Available online at: https://doi.org/10.4161/cbt.19291.)

Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA, et al: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA 2005;294:1233–1239. (Available onlinbe at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16160131.)

Zietman AL, Grocela J, Zehr E, Kaufman DS, Young RH, Althausen AF, et al: Selective bladder conservation using transurethral resection, chemotherapy, and radiation: Management and consequences of Ta, T1, and Tis recurrence within the retained bladder. Urology 2001;58(3):380–385. (Available online at: http://www.ncbi.nlm.nih.gov/pubmed/11549485.)

Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al: Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. J Clin Oncol 2010;28(7):1106–1111. (Available online at: https://doi.org/10.1200/JCO.2009.25.8475.)

Zietman AL, Sacco D, Skowronski U, Gomery P, Kaufman DS, Clark JA, et al: Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: Results of a urodynamic and quality of life study on long-term survivors. J Urol 2003;170(5):1772–1776. (Available online at: https://doi.org/10.1097/01.ju.0000093721.23249.c3.)

Neurophysiology and Pharmacology of the Lower Urinary Tract

27

Karl-Erik Andersson, MD, PhD

INTRODUCTION

The bladder, in concert with the urethra and the pelvic floor, is responsible for storage and periodic expulsion of urine. The integrated function of these components of the lower urinary tract (LUT) is dependent on a complex control system in the brain, spinal cord, and peripheral ganglia, and on local regulatory factors (de Groat and Yoshimura, 2001, 2006, 2015). Dysfunction of the central nervous control systems or of the components of the LUT can produce voiding difficulties and retention of urine, or different types of urinary incontinence (mainly urgency and stress incontinence), or the symptom complex of the "overactive bladder" (OAB), characterized by urgency and frequency with or without urgency incontinence, often with nocturia (Abrams et al, 2002).

Pharmacologic treatment of urinary incontinence and LUT symptoms (LUTSs) including OAB is a main option, and several drugs with different modes and sites of action, have been tried (Andersson, 2016; Andersson et al, 2013; Andersson and Wein, 2004; Bechis et al, 2015; Sacco and Bientinesi, 2015). However, to be able to optimize treatment, knowledge about the mechanisms of micturition and of the targets for treatment is necessary. Theoretically, failure to store urine can be improved by agents that decrease detrusor activity and increase bladder capacity, and/or increase outlet resistance.

This chapter briefly reviews the normal nervous control of the LUT and of some therapeutic principles used in the treatment of urinary incontinence.

NEURAL CIRCUITS CONTROLLING STORAGE AND EXPULSION OF URINE

Normal micturition occurs in response to afferent signals from the LUT (Birder and Andersson, 2013; de Groat and Yoshimura, 2006, 2015; Fowler et al, 2008). Bladder filling and voiding are both controlled by neural circuits in the brain, spinal cord, and peripheral ganglia. These circuits coordinate the activity of the smooth muscle in the detrusor and urethra with that of the striated muscles in the urethral sphincter and pelvic floor. Suprapontine influences are believed to act as on/off switches to shift the LUT between the two modes of operation: storage and elimination. In adults, urine storage and voiding are under voluntary control and depend on learned behavior. In infants, however, these switching mechanisms function in a reflex manner to produce involuntary voiding. In adults, injuries or diseases of the central nervous system (CNS) can disrupt the voluntary control of micturition and cause the reemergence of reflex micturition, resulting in OAB and detrusor overactivity (DO). Because of the complexity of the CNS control of the LUT, OAB and DO can occur as a result of a variety of neurological disorders as well as changes in the peripheral innervation and smooth and skeletal muscle components (Andersson and Arner, 2004; Andersson and Wein, 2004).

Filling of the bladder and voiding involve a complex pattern of afferent and efferent signaling in parasympathetic (pelvic nerves), sympathetic (hypogastric nerves), and somatic (pudendal nerves) pathways. These pathways constitute reflexes, which either keep the bladder in a relaxed state, enabling urine storage at low intravesical pressure, or which initiate bladder emptying by relaxing the outflow region and contracting the detrusor. Integration of the autonomic and somatic efferents that results in contraction of the detrusor muscle is preceded by a relaxation of the outlet region, thereby facilitating bladder emptying. On the contrary, during the storage phase, the detrusor muscle is relaxed and the outlet region is contracted to maintain continence.

PARASYMPATHETIC PATHWAYS

The sacral parasympathetic pathways mediate contraction of the detrusor smooth muscle and relaxation of the outflow region. The preganglionic **parasympathetic** neurons are located to the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2–S4. The axons pass through the pelvic nerves and synapse with the postganglionic nerves either in the pelvic plexus, in ganglia on the surface of the bladder (vesical ganglia), or within the walls of the bladder and urethra (intramural ganglia). The ganglionic neurotransmission is predominantly mediated by acetylcholine acting on nicotinic receptors, although the transmission can be modulated by adrenergic, muscarinic, purinergic, and peptidergic presynaptic receptors. The postganglionic neurons in the pelvic nerve mediate the excitatory input to the normal human detrusor smooth muscle by releasing acetylcholine acting on muscarinic receptors (see discussion later in the chapter). However, an atropine-resistant (nonadrenergic, noncholinergic [NANC]) contractile component is regularly found in the bladders of most animal species. Such a component can also be demonstrated in functionally and morphologically altered human bladder tissue (O'Reilly et al, 2002), but it contributes to a very low percentage of normal detrusor contraction (Andersson and Wein, 2004). Adenosine triphosphate (ATP) is the most important mediator of the NANC contraction, although the involvement of other transmitters cannot be ruled out (Andersson and Wein, 2004). The pelvic nerve also conveys parasympathetic neurons to the outflow region and the urethra. These nerves exert an inhibitory effect on the smooth muscle, by releasing nitric oxide and other transmitters (Andersson and Wein, 2004).

SYMPATHETIC PATHWAYS

The *sympathetic* innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoracolumbar region (T10–L2) of the spinal cord. The axons leave the spinal cord via the splanchnic nerves and either travel through the inferior mesenteric ganglia (IMF) and the hypogastric nerve or pass through the paravertebral chain to the lumbosacral sympathetic chain ganglia and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric nerve and the pelvic nerve. The ganglionic sympathetic transmission is, like the parasympathetic preganglionic transmission, predominantly mediated by acetylcholine acting on nicotinic receptors. Some preganglionic terminals synapse with the postganglionic cells in the paravertebral ganglia or in the IMF, while other terminals synapse closer to the pelvic organs, and short postganglionic neurons innervate the target organs. Thus, the hypogastric and pelvic nerves contain both pre- and postganglionic fiber. The predominant effect of the sympathetic innervation is to contract the bladder base and the urethra. In addition, the sympathetic innervation inhibits the parasympathetic pathways at spinal and ganglionic levels. In the human bladder, electrical field stimulation in vitro causes nerve release of noradrenaline, which in the normal detrusor causes relaxation. However, the importance of the sympathetic innervation for relaxation of the human detrusor has never been established. In contrast, in several animal species, the adrenergic innervation has been demonstrated to mediate relaxation of the detrusor during filling (Andersson and Arner, 2004).

SOMATIC PATHWAYS

The **somatic** innervation of the urethral rhabdosphincter and of some perineal muscles (eg, compressor urethrae and urethrovaginal sphincter) is provided by the pudendal nerve. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2–S4) in a region called **Onuf's (Onufrowicz's) nucleus** (Thor and de Groat, 2010; Thor and Donatucci, 2004).

AFFERENT PATHWAYS

The **afferent** nerves to the bladder and urethra originate in the dorsal root ganglia at the lumbosacral level of the spinal cord and travel via the pelvic nerve to the periphery (de Groat and Yoshimura, 2010; Kanai and Andersson, 2010). Some afferents originate in dorsal root ganglia at the thoracolumbar level and travel peripherally in the hypogastric nerve. The afferent nerves to the striated muscle of the external urethral sphincter travel in the pudendal nerve to the sacral region of the spinal cord. The most important afferents for the micturition process are myelinated Aδ-fibers and unmyelinated C-fibers traveling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall. The Aδ-fibers respond to passive distension and active contraction, thus conveying information about bladder filling. The activation threshold for Aδ-fibers is 5–15 mm H_2O. This is the intravesical pressure at which humans report the first sensation of bladder filling. C-fibers have a high mechanical threshold and respond primarily to chemical irritation of the bladder urothelium/suburothelium or to cold. Following chemical irritation, the C-fiber afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension. These fibers are normally inactive and are therefore termed "silent fibers." Afferent information about the amount of urine in the bladder is continuously conveyed to the mesencephalic periaqueductal gray (PAG), and from there to the pontine micturition center (PMC), also called **Barrington's nucleus** (Holstege, 2005; Kuipers et al, 2006).

AFFERENT SIGNALING FROM THE UROTHELIUM/SUBUROTHELIUM

Recent evidence suggests that the urothelium/suburothelium may serve not only as a passive barrier but also as a specialized sensory and signaling unit, which, by producing nitric oxide, ATP, and other mediators, can control the activity in afferent nerves, and thereby the initiation of the micturition reflex (Andersson, 2002; Birder and Andersson, 2013; Birder and de Groat, 2007; de Groat, 2004). The urothelium has been shown to express, for example, nicotinic, muscarinic, tachykinin, adrenergic, bradykinin, and transient receptor potential (TRP) receptors (Birder and Andersson, 2013; Birder and de Groat, 2007). Low pH, high K^+, increased osmolality, and low temperatures can all influence afferent nerves, possibly via effects on the vanilloid receptor (capsaicin [CAP]-gated ion channel, TRPV1), which is expressed in both afferent nerve terminals and urothelial cells (Birder et al, 2001, 2002). A network of interstitial cells, extensively linked by Cx43-containing gap junctions, was found to be located beneath the urothelium in the human bladder (Brading and McCloskey, 2005; McCloskey, 2010; Sui et al, 2002, 2004). This interstitial cellular network was suggested to operate as a functional syncytium, integrating signals and responses in the bladder wall. The firing of suburothelial afferent nerves, conveying sensations and regulating the threshold for bladder activation, may be modified by both inhibitory (eg, nitric oxide) and stimulatory (eg, ATP, tachykinins, prostanoids) mediators. ATP, generated by the urothelium, has been suggested as an important mediator of urothelial signaling (Andersson, 2002). Supporting such a view, intravesical ATP induces DO in conscious rats (Pandita and Andersson, 2002). Furthermore, mice lacking the $P2X_3$ receptor were shown to have hypoactive bladders (Cockayne et al, 2000; Vlaskovska et al, 2001). Interstitial cells can also be demonstrated within the detrusor muscle (Brading and McCloskey, 2005; McCloskey, 2010). They may be involved in impulse transmission, but their role has not been clarified.

There seem to be other, thus far unidentified, factors in the urothelium that could influence bladder function (Andersson and Wein, 2004). Even if these mechanisms can be involved in, for example, the pathophysiology of OAB, their functional importance remains to be established.

NEURAL CONTROL OF BLADDER FILLING

During the storage phase, the bladder must relax in order to maintain a low intravesical pressure. Urine storage is regulated by two separate storage reflexes, one of which is sympathetic (autonomic) while the other is somatic (Thor and Donatucci, 2004). The **sympathetic storage reflex** (pelvic-to-hypogastric reflex) is initiated as the bladder distends (myelinated Aδ-fibers) and the generated afferent activity travels in the pelvic nerves to the spinal cord. Within the spinal cord, sympathetic firing from the lumbar region (L1–L3) is initiated, which, by effects at the ganglionic level, decreases excitatory parasympathetic input to the bladder. Postganglionic neurons release noradrenaline, which facilitates urine storage by stimulating β_3-adrenoceptors (ARs) in the detrusor smooth muscle (see discussion later). As mentioned previously, there is little evidence for a functionally important sympathetic innervation of the human detrusor, which differs from findings in several animal species. The sympathetic innervation of the human bladder is found mainly in the outlet region, where it mediates contraction. During micturition, this sympathetic reflex pathway is markedly inhibited via supraspinal mechanisms to allow the bladder to contract and the urethra to relax. Thus, the Aδ afferents and the sympathetic efferent fibers constitute a vesicospinovesical storage reflex, which maintains the bladder in a relaxed mode while the proximal urethra and bladder neck are contracted.

In response to a sudden increase in intra-abdominal pressure, such as during a cough, laugh, or sneeze, a more rapid **somatic storage reflex** (pelvic-to-pudendal reflex), also called the "guarding" or "continence reflex," is initiated. The evoked afferent activity travels along myelinated Aδ afferent nerve fibers in the pelvic nerve to the sacral spinal cord, where efferent somatic urethral motor neurons, located in the nucleus of Onuf, are activated. Afferent information is also conveyed to the PAG and from there to the PMC (the L region). From this center, impulses are conveyed to the motor neurons in the nucleus of Onuf. Axons from these neurons travel in the pudendal nerve and release acetylcholine, which activates nicotinic cholinergic receptors on the rhabdosphincter, which contracts. This pathway is tonically active during urine storage. During sudden abdominal pressure increases, however, it becomes dynamically active to contract the rhabdosphincter. During micturition, this reflex is strongly inhibited via spinal and supraspinal mechanisms to allow the rhabdosphincter to relax and permit urine passage through the urethra. In addition to this spinal somatic storage reflex, there is also supraspinal input from the pons, which projects directly to the nucleus of Onuf and is important for voluntary control of the rhabdosphincter (Blok et al, 1997; Holstege, 2005; Sugaya et al, 2005).

NEURAL CONTROL OF BLADDER EMPTYING

Vesicobulbovesical Micturition Reflex

Electrophysiological experiments in cats and rats provide evidence for a voiding reflex mediated through a vesicobulbovesical pathway involving neural circuits in the pons, which constitute the PMC. Other regions in the brain, important for micturition, include the hypothalamus and cerebral cortex (Fowler et al, 2008; Griffiths, 2004; Griffiths et al, 2005; Holstege, 2005). Bladder filling leads to increased activation of tension receptors within the bladder wall, and thus to increased afferent activity in Aδ-fibers. These fibers project on spinal tract neurons, mediating increased sympathetic firing to maintain continence, as discussed earlier (storage reflex). In addition, the spinal tract neurons convey the afferent activity to more rostral areas of the spinal cord and the brain. As mentioned previously, one important receiver of the afferent information from the bladder is the PAG in the rostral brain stem (Fowler et al, 2008; Holstege, 2005; Kuipers et al, 2006). The PAG receives information both from afferent neurons in the bladder and from more rostral areas in the brain, that is, the cerebral cortex and hypothalamus. This information is integrated in the PAG and the medial part of the PMC (the M region), which also controls the descending pathways in the micturition reflex. Thus, PMC can be regarded as a switch in the micturition reflex, inhibiting parasympathetic activity in the descending pathways when there is low activity in the afferent fibers, and activating the parasympathetic pathways when the afferent activity reaches a certain threshold. The threshold is believed to be set by the inputs from more rostral regions in the brain. In cats, lesioning of regions above the inferior colliculus usually facilitates micturition by elimination of inhibitory inputs from more rostral areas of the brain. On the other hand, transections at a lower level inhibit micturition. Thus, the PMC seems to be under a tonic inhibitory control. A variation of the inhibitory input to PMC results in a variation of bladder capacity. Experiments on rats have shown that the micturition threshold is regulated by, for example, γ-aminobutyric acid (GABA)-ergic inhibitory mechanisms in the PMC neurons.

Vesicospinovesical Micturition Reflex

Spinal lesions rostral to the lumbosacral level interrupt the vesicobulbovesical pathway and abolish the supraspinal and voluntary control of micturition (Anderson and Wein, 2004). This results initially in an areflexic bladder accompanied by urinary retention. An automatic vesicospinovesical micturition reflex develops slowly, although voiding is generally insufficient as a result of bladder–sphincter dyssynergia, that is, simultaneous contraction of bladder and urethra. It has been demonstrated in chronic spinal cats that the afferent limb of this reflex is conveyed through unmyelinated C-fibers, which seldom respond to bladder distension, suggesting changed properties of the afferent receptors in the bladder. Accordingly, the micturition reflex in chronic spinal cats is blocked by CAP, which blocks C-fiber-mediated neurotransmission.

CNS TARGETS FOR PHARMACOLOGIC INTERVENTION

Anatomically, several CNS regions may be involved in micturition control: supraspinal structures, such as the cortex and diencephalon, midbrain, and medulla, and also spinal structures (Fowler et al, 2008; Fowler and Griffiths, 2010; Griffiths, 2004; Griffiths et al, 2005; Holstege, 2005; Sugaya et al, 2005). Several transmitters are involved in the micturition reflex pathways described earlier and may be targets for drugs aimed for control of micturition (de Groat and Yoshimura, 2001). However, few drugs with a CNS site of action have been developed (Andersson and Pehrson, 2003; Yoshimura et al, 2014).

Opioid Receptors

Endogenous opioid peptides and corresponding receptors are widely distributed in many regions in the CNS of importance for micturition control (de Groat and Yoshimura, 2001). It has been well established that morphine, given by various routes of administration to animals and humans, can increase bladder capacity or block bladder contractions. Furthermore, given intrathecally to anesthetized rats and intravenously to humans, the μ-opioid receptor antagonist, naloxone, has been shown to stimulate micturition, suggesting that a tonic activation of μ-opioid receptors has a depressant effect on the micturition reflex. However, intrathecal naloxone was not effective in stimulating micturition in conscious rats at doses blocking the effects of intrathecal morphine (Andersson and Wein, 2004).

Morphine given intrathecally was effective in patients with DO due to spinal cord lesions, but it was associated with side effects, such as nausea and pruritus. Further side effects of opioid receptor agonists include respiratory depression, constipation, and abuse (Andersson and Wein, 2004). Attempts have been made to reduce these side effects by increasing selectivity toward one of the different opioid receptor types. At least three different opioid receptors—μ, δ, and κ—bind stereospecifically with morphine and have been shown to interfere with voiding mechanisms. Theoretically, selective receptor actions, or modifications of effects mediated by specific opioid receptors, may have useful therapeutic effects for micturition control.

Tramadol is a well-known analgesic drug. By itself, it is a weak μ-receptor agonist, but it is metabolized to several different compounds, some of which are almost as effective as morphine at the μ-receptor. However, the drug also inhibits serotonin (5-HT) and noradrenaline reuptake (Raffa and Friderichs, 1996). This profile is of interest, since both μ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of DO/OAB.

When tramadol is given to a normal, awake rat, the most conspicuous changes in the cystometrogram are increases in threshold pressure and bladder capacity. Naloxone can almost completely inhibit these effects (Pandita et al, 2003). However, there are differences between the effects of tramadol and morphine. Morphine has a very narrow range between the doses causing inhibition of micturition and those increasing bladder capacity and evoking urinary retention. Tramadol has effects over a much wider range of doses, which means that it could be more useful therapeutically for micturition control. It may be speculated that the difference is dependent on the simultaneous influence of the 5-HT and noradrenaline uptake inhibition (Pandita et al, 2003).

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction (Pehrson et al, 2003). Tramadol also inhibited DO induced by apomorphine in rats (Pehrson and Andersson, 2003)—a model of bladder dysfunction in Parkinson's disease. Whether tramadol may have a clinically useful effect on DO/OAB remains to be studied in randomized controlled clinical trials (RCTs).

Safarinejad and Hosseini (2006) evaluated in a double-blind, placebo-controlled, randomized study, the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years and older were given 100 mg tramadol sustained release every 12 hours for 12 weeks. Clinical evaluation was performed at baseline and every 2 weeks during treatment. Tramadol significantly ($p < .001$) reduced the number of incontinence periods per 24 hours from 3.2 ± 3.3 to 1.6 ± 2.8) and induced improvement in urodynamic parameters. The main adverse event was nausea. It was concluded that in patients with nonneurogenic DO, tramadol provided beneficial clinical and urodynamic effects. However, the study was later retracted because of unacceptable statistical errors (Safarinejad and Hosseini, 2006; retracted 2014).

Serotonin (5-HT) Mechanisms

Lumbosacral autonomic, as well as somatic, motor nuclei (Onuf's nuclei) receive a dense serotonergic input from the raphe nuclei, and multiple 5-HT receptors have been found at sites where afferent and efferent impulses from and to the LUT are processed (Ramage, 2006). The main receptors shown to be implicated in the control of micturition are the 5-HT$_{1A}$, 5-HT$_2$, and 5-HT$_7$ receptors (Ramage, 2006). There is some evidence in rats for serotonergic facilitation of voiding; however, the descending pathway is essentially an inhibitory circuit, with 5-HT as a key neurotransmitter.

It has been speculated that selective serotonin reuptake inhibitors (SSRIs) may be useful for treatment of DO/OAB. On the other hand, there are reports suggesting that the SSRIs in patients without incontinence can cause incontinence, particularly in the elderly, and one of the drugs (sertraline) seemed to be more prone to produce urinary incontinence than the others (Movig et al, 2002). Patients exposed to serotonin uptake inhibitors had an increased risk (15 out of 1000 patients) for developing urinary incontinence. So far, there have been no RCTs demonstrating the value of SSRIs in the treatment of DO/OAB.

Duloxetine is a combined noradrenaline and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function (Katofiasc et al, 2002; Thor et al, 1995). Bladder capacity was also increased in this model, with both effects mediated centrally through both motor efferent and sensory afferent modulation. The effects of duloxetine was studied in a placebo-controlled study comprising women with OAB (Steers et al, 2007) and was, compared with placebo, shown to cause significant improvements or decreases in voiding and incontinence episodes, for increases in the daytime voiding intervals, and for improvement in quality-of-life (I-QoL) scores. Urodynamic studies showed no significant increase in maximum cystometric capacity or in the volume threshold for DO.

GABA Mechanisms

In both the brain and the spinal cord, GABA has been identified as a main inhibitory transmitter (de Groat and Yoshimura, 2001). GABA functions appear to be triggered by binding of GABA to its inotropic receptors, GABA$_A$ and GABA$_C$, which are ligand-gated chloride channels, and its metabotropic receptor, GABA$_B$ (Chebib and Johnston, 1999). Since blockade of GABA$_A$ and GABA$_B$ receptors in the spinal cord and brain (Pehrson and Andersson, 2002) stimulated rat micturition, an endogenous activation of GABA$_{A+B}$ receptors may be responsible for continuous inhibition of the micturition reflex within the CNS. In the spinal cord, GABA$_A$ receptors are more numerous than GABA$_B$ receptors, except for the dorsal horn, where GABA$_B$ receptors predominate.

Experiments using conscious and anesthetized rats demonstrated that exogenous GABA, muscimol (GABA$_A$ receptor agonist), and baclofen (GABA$_B$ receptor agonist) given intravenously, intrathecally, or intracerebroventricularly inhibit micturition (Pehrson et al, 2002). Baclofen given intrathecally attenuated oxyhemoglobin-induced DO, suggesting that the inhibitory actions of GABA$_B$ receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium (Pehrson et al, 2002).

Stimulation of the PMC results in an immediate relaxation of the external striated sphincter and a contraction of the detrusor muscle of the bladder demonstrated in cats a direct pathway from the PMC to the dorsal gray commissure of the sacral cord (Blok et al, 1997). It was suggested that the pathway produced relaxation of the external striated sphincter during micturition via inhibitory modulation by GABA neurons of the motoneurons in the sphincter of Onuf (Blok et al, 1997). In rats, intrathecal baclofen and muscimol ultimately produced dribbling urinary incontinence (Pehrson et al, 2002).

Thus, normal relaxation of the striated urethral sphincter is probably mediated via GABA$_A$ receptors (Pehrson et al, 2002; Pehrson and Andersson, 2002), with GABA$_B$ receptors having a minor influence on motoneuron excitability (Rekling et al, 2000).

Gabapentin was originally designed as an anticonvulsant GABA mimetic capable of crossing the blood–brain barrier (Maneuf et al, 2003). The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial (Maneuf et al, 2003), even if it has been suggested that it acts by binding to a subunit of the $\alpha_2\delta$ unit of voltage-dependent calcium channels. Gabapentin is also widely used not only for seizures and neuropathic pain but also for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

In a pilot study, Carbone et al (2003) reported on the effect of gabapentin on neurogenic DO. These investigators found a positive effect on symptoms and significant improvement in urodynamic parameters after treatment with gabapentin and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and nonneurogenic DO. Kim et al (2004) studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other $\alpha_2\delta$ ligands (eg, pregabalin and analogs) will offer new therapeutic alternatives.

Noradrenaline Mechanisms

Noradrenergic neurons in the brainstem project to the sympathetic, parasympathetic, and somatic nuclei in the lumbosacral spinal area. Bladder activation through these bulbospinal noradrenergic pathways may involve excitatory α_1-ARs, which can be blocked by **α_1-AR antagonists** (Yoshiyama et al, 2000). In rats undergoing continuous cystometry, doxazosin, given intrathecally, decreased micturition pressure, both in normal rats and in animals with postobstruction bladder hypertrophy. The effect was much more pronounced in the animals with hypertrophied OABs. Doxazosin given intrathecally, but not intra-arterially, to spontaneously hypertensive rats exhibiting bladder overactivity, normalized bladder activity (Persson et al, 1998). It was suggested that doxazosin has a site of action at the level of the spinal cord and ganglia.

A central site of action for α_1-AR antagonists has been discussed as an explanation for the beneficial effects of these drugs in LUTS (especially storage symptoms) associated with benign prostatic hyperplasia (BPH) (Andersson and Gratzke, 2007; Andersson and Wein, 2004).

Dopamine Mechanisms

Patients with Parkinson's disease may have neurogenic DO, possibly as a consequence of nigrostriatal dopamine depletion and failure to activate inhibitory D_1 receptors (Andersson, 2004). However, other dopaminergic systems may activate D_2 receptors, facilitating the micturition reflex. Apomorphine, which activates both D_1 and D_2 receptors, induced bladder overactivity in anesthetized rats via stimulation of central dopaminergic receptors. The effects were abolished by infracollicular transection of the brain and by prior intraperitoneal administration of the centrally acting dopamine receptor blocker, spiroperidol. It has been shown that the DO induced by apomorphine in anesthetized rats resulted from synchronous stimulation of the micturition centers in the brainstem and spinal cord, and that the response was elicited by stimulation of both dopamine D_1 and D_2 receptors. Blockade of central dopamine receptors may be expected to influence voiding; however, the therapeutic potential of drugs having this action has not been established (Andersson and Wein, 2004).

NK1 Receptor Mechanisms

The main endogenous tachykinins, substance P, neurokinin A (NKA), and neurokinin B (NKB), and their preferred receptors, NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control (Covenas et al, 2003; Lecci and Maggi, 2001; Saffroy et al, 2003).

Aprepitant, an NK1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting (Massaro and Lenz, 2005), significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence, as shown in a well-designed pilot RCT (Green et al, 2006). Aprepitant was generally well tolerated, and the incidence of side effects, including dry mouth, was low. Another NK1 receptor antagonist, **serlopitant**, significantly decreased daily micturitions but did not offer advantages in efficacy compared with tolterodine (Frenkl et al, 2010). The results of these studies suggest that NK1 receptor antagonism holds promise as a potential treatment approach for OAB, but so far, the drugs available have not been very effective.

PERIPHERAL TARGETS FOR PHARMACOLOGIC INTERVENTION

There are many possible peripheral targets for pharmacologic control of bladder function (Andersson and Arner, 2004). Although many effective drugs that target these systems are available, most of them are less useful in the clinical situation because of the lack of selectivity for LUT, which may result in intolerable side effects.

Muscarinic Receptors

Muscarinic receptors comprise five subtypes, M_1–M_5, encoded by five distinct genes, and in both animal and human bladders, the mRNAs for all muscarinic receptor subtypes have been demonstrated, with a predominance of mRNAs encoding M_2 and M_3 receptors. These receptors are also functionally coupled to G proteins, but the signal transduction systems vary (Andersson, 2011; Andersson and Arner, 2004; Giglio and Tobin, 2009).

Detrusor smooth muscle contains muscarinic receptors mainly of the M_2 and M_3 subtypes. The M_3 receptors in the human bladder are the most important for detrusor contraction (Andersson and Wein, 2004). In the human detrusor, Schneider et al (2004) confirmed that the muscarinic receptor subtype mediating carbachol-induced contraction was the M_3 receptor, and they also demonstrated that the L-type calcium channel blocker, nifedipine, almost completely inhibited carbachol-induced detrusor contraction, whereas an inhibitor of store-operated Ca^{2+} channels caused little inhibition. The ρ-kinase inhibitor, Y27632, produced a concentration-dependent attenuation of the carbachol-induced contractile responses. Schneider et al (2004) concluded that carbachol-induced contraction of human detrusor is mediated via M_3 receptors, and furthermore, largely depends on transmembrane Ca^{2+} flux through nifedipine-sensitive calcium channels as well as activation of the ρ-kinase pathway. These conclusions were supported by Takahashi et al (2004), who found that in human detrusor muscle, carbachol induces contraction, not only by increasing $[Ca^{2+}]$ but also by increasing the Ca^{2+} sensitivity of the contractile apparatus in a ρ-kinase and protein kinase C-dependent manner.

It has been suggested that M_2 receptors may oppose sympathetically mediated smooth-muscle relaxation, mediated by β-ARs (Hegde, 1997). M_2 receptor stimulation may also activate nonspecific cation channels and inhibit K_{ATP} channels through activation of protein kinase C. However, the functional role for the M_2 receptors in the normal bladder has not been clarified, but in certain disease states, M_2 receptors may contribute to contraction of the bladder. Thus, in the denervated rat bladder, M_2 receptors, or a combination of M_2 and M_3 receptors, mediate contractile responses. Both types of receptor seemed to act in a facilitatory manner to mediate contraction (Braverman et al, 2002). In obstructed, hypertrophied rat bladders, there was an increase in total M_2 receptor density but a reduction in M_3 receptor density (Braverman and Ruggieri, 2003). The functional significance of this change for voiding function has not been established. Pontari et al (2004) analyzed bladder muscle specimens from patients with neurogenic bladder dysfunction to determine whether the muscarinic receptor subtype mediating contraction shifts from M_3 to the M_2 receptor subtype, as found in the denervated, hypertrophied rat bladder. They concluded that although normal detrusor contractions are mediated by the M_3 receptor subtype, in patients with neurogenic bladder dysfunction, contractions can be mediated by the M_2 receptors.

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as M_2 in the rabbit and rat, and M_4 in the guinea pig, rat, and human bladder. Prejunctional facilitatory muscarinic receptors appear to be of the M_1 subtype in the rat and rabbit urinary bladder (Andersson and Arner, 2004). Prejunctional muscarinic facilitation has also been detected in human bladders. The muscarinic facilitatory mechanism seems to be upregulated in OABs from chronic spinal cord-transected rats. The facilitation in these preparations is primarily mediated by M_3 muscarinic receptors (Somogyi et al, 2003).

Muscarinic receptors have also been demonstrated in the urothelium and in the suburothelium (Bschleipfer et al, 2007; Chess-Williams, 2002; Mansfield et al, 2005), but their functional importance has not been clarified. It has been suggested that they may be involved in the release of an unknown inhibitory factor (Chess-Williams, 2002), or they may be directly involved in afferent signaling, and thus a target for antimuscarinic agents, explaining part of the efficacy of these drugs in DO/OAB (Andersson, 2004; Andersson and Yoshida, 2003; Kim et al, 2005; Yokoyama et al, 2005).

Antimuscarinics

In general, antimuscarinics can be divided into tertiary and quaternary amines (Abrams and Andersson, 2007; Guay, 2003). They differ with regard to lipophilicity, molecular charge, and even molecular size, as tertiary compounds generally have higher lipophilicity and molecular charge than quaternary agents. **Atropine**, **darifenacin**, **fesoterodine** (and its active metabolite 5-hydroxymethyltolterodine), **oxybutynin**, **propiverine**, **solifenacin**, and **tolterodine** are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the CNS, dependent on their individual physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood–brain barrier, but for some of the drugs, this is counteracted by active transport out of the CNS. Quaternary ammonium compounds, like propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects (Guay, 2003). They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, tachycardia, and dryness of the mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites (Guay, 2003). The most commonly involved P450 enzymes are CYP2D6 and CYP3A4. The metabolic conversion creates a risk for drug–drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration/effect of the antimuscarinic and/or interacting drug. Antimuscarinics secreted by the renal tubules (eg, trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism.

Antimuscarinics are still the most widely used treatment for urgency and urgency incontinence (Andersson et al, 2013). However, currently used drugs lack selectivity for the bladder, and effects on other organ systems may result in side effects, which limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow-angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained, if the subtype(s) mediating bladder contraction, and those producing the main side effects of antimuscarinic drugs, were different. Unfortunately, this does not seem to be the case. One way to avoid many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical in only a limited number of patients.

A. Clinical Efficacy

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned (Herbison et al, 2003). However, large meta-analyses of studies performed with the currently most widely used drugs (Chapple et al, 2005, 2008; Novara et al, 2008) clearly show that antimuscarinics are of significant clinical benefit.

None of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, or trospium) is ideal as a first-line treatment for *all* OAB/DO patients. Optimal treatment should be individualized, implying that the patient's comorbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration (Chapple et al, 2008).

B. Tolerability and Safety

An extensive literature supports the theory that antimuscarinics for the treatment of OAB symptoms are generally well tolerated. The adverse effect profiles of the different drugs are determined by their organ and muscarinic receptor subtype selectivities and pharmacokinetic parameters. The most commonly reported adverse effects are dry mouth, constipation, headache, and blurred vision.

Among the more serious concerns related to antimuscarinic use is the risk of cardiac adverse effects, particularly increases in heart rate and QT prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes). It should be emphasized that QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather are linked to inhibition of the hERG potassium channel in the heart (Roden, 2004). Thus, QT prolongation is not a class effect of antimuscarinics. In general, the cardiovascular safety for antimuscarinic drugs seems to be good. However, the potential of the different agents to increase heart rate or to prolong the QT time has not been extensively explored. Differences between the drugs cannot be excluded, but risk assessments based on available evidence are not possible (Andersson et al, 2011).

Another concern is that antimuscarinic drugs commonly used to treat OAB can be associated with CNS side effects, including cognitive dysfunction, memory impairment, dizziness, fatigue, and headache. With the exception for oxybutynin, CNS-related side effects are not commonly found when investigated. The potential to cause CNS-related adverse effects may differ between drugs, but in the absence of comparative trials, relative risk assessments are not possible.

For detailed discussion of the clinical efficacy, tolerability, and safety of the individual antimuscarinics, see Andersson et al (2009b).

▶ Adrenergic Receptors

A. α-ARs

Most investigators agree that there is a low expression of α-ARs in the human detrusor (Michel, 2006). Malloy et al (1998) found that two-thirds of the α-AR mRNA expressed was α_{1D}, and one-third was α_{1A} (there was no α_{1B}). It has been suggested that a change of subtype distribution may be produced by outflow obstruction. Nomiya and Yamaguchi (2003) confirmed the low expression of α-AR mRNA in normal human detrusor, and further demonstrated, in contrast to data from animal experiments (Hampet et al, 2000), that there was no upregulation of any of the adrenergic receptors with obstruction. In addition, in functional experiments, they found a small response to phenylephrine at high drug concentrations with no difference between normal and obstructed bladders. Thus, in the obstructed human bladder, there seems to be no evidence for α-AR upregulation or change in subtype, although this finding was challenged by Bouchelouche et al (2005), who found an increased response to α_1-AR stimulation in obstructed bladders. Whether this would mean that the α_{1D}-ARs in the detrusor muscle are responsible for DO or OAB is unclear.

Sugaya et al (2002) investigated the effects of intrathecal tamsulosin (blocking $\alpha_{1A/D}$-ARs) and naftopidil (blocking preferably on α_{1D}-ARs) on isovolumetric bladder contractions in rats. Intrathecal injection of tamsulosin or naftopidil transiently abolished these contractions. The amplitude of contraction was decreased by naftopidil but not by tamsulosin. It was speculated that in addition to the antagonistic action of these agents on the α_{1A}-ARs of prostatic smooth muscle, both agents (especially naftopidil) may also act on the lumbosacral cord (α_{1D}-ARs). This observation is of interest considering the findings that in the human spinal cord, α_{1D}-AR mRNA predominated overall (Smith et al, 1999). Ikemoto et al (2003) gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Although naftopidil monotherapy decreased the I-PSS for storage symptoms, tamsulosin monotherapy decreased the I-PSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α_1-AR subtypes between the drugs) could not be reproduced in a randomized head-to-head comparison between the drugs (Gotoh et al, 2005).

B. β-ARs

It has been known for a long time that isoprenaline, a non-subtype-selective β-AR agonist, can relax bladder smooth muscle (Andersson, 1993). Even if the importance of β-ARs for human bladder function remains to be established (Andersson and Arner, 2004), this does not exclude the possibility that they can be useful therapeutic targets. All three subtypes of β-ARs (β_1, β_2, and β_3) can be found in the detrusor muscle of most species, including humans (Michel and Vrydag, 2006) and also in the human urothelium (Otsuka et al, 2008). However, the expression of β_3-AR mRNA (Nomiya and Yamaguchi, 2003; Michel and Vrydag, 2006) and functional evidence indicate a predominant role for this receptor in both normal and neurogenic bladders (Michel and Vrydag, 2006). The human detrusor also contains β_2-ARs, and most probably both receptors are involved in the physiological effects (relaxation) of noradrenaline in the bladder (Andersson and Arner, 2004; Michel and Vrydag, 2006).

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder K+ channels, particularly BK_{Ca} channels, may be more important in β-AR-mediated relaxation than cAMP (Frazier et al, 2008). β_3-AR agonists have generally been considered to relieve OAB symptoms by relaxing detrusor muscle, inhibiting spontaneous contractile activity in the detrusor (in vitro—microcontractions; in vivo—nonvoiding contractions), and reducing bladder afferent activity (Igawa and Michel, 2013). However, Gillespie and colleagues have questioned the accepted view on the mode and site of action of β_3-AR agonists (Gillespie et al, 2015a,b), and suggested that effects on neither spontaneous microcontractions, nor on nonvoiding contractions in for example, obstructed rats, can fully explain the effects of mirabegron. Assuming that acetylcholine (ACh) release from cholinergic terminals during bladder filling contributes to OAB symptoms, the finding that activation of pre-junctional β_3-ARs may downregulate ACh release resulting in an inhibitory control of parasympathetic activity, may be of importance (Rouget et al, 2014; D'Agostino et al, 2015).

Since β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated (Murakami et al, 2007; Otsuka et al, 2008). Murakami et al (2007) found that the relaxation responses of the detrusor were not influenced by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka et al (2008). However, to what extent a urothelial signaling pathway contributes in vitro and in vivo to the relaxant effects of β-AR agonists in general, and β_3-AR agonists specifically, remains to be elucidated.

The in vivo effects of β_3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β_3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume (Igawa et al, 2010).

A number of β_3-AR-selective agonists are currently being evaluated as potential treatment for OAB, but so far the only drug approved for treatment in humans is mirabegron. The effects of mirabegron in men and women with OAB have been summarized in several recent reviews (Chapple et al, 2014; Cui et al, 2014; Rossanese et al, 2015; Samuelsson et al, 2015; Warren et al, 2016), and also in men with both voiding and OAB symptoms (Suarez et al, 2013; Otsuki et al, 2013).

C. Mirabegron

Takusagawa et al (2012) found that mirabegron was rapidly absorbed after oral administration. It circulates in the plasma as the unchanged form, its glucuronic acid conjugates and other metabolites. Of the administered dose, 55% is excreted in urine, mainly as the unchanged form, and 34% is recovered in feces, almost entirely as the unchanged form. Mirabegron is highly lipophilic and is metabolized in the liver via multiple pathways, mainly by cytochrome P450 3A4 and 2D6 (CYP2D6) (van Gelderen et al, 2009). In a phase I pharmacokinetic study, 16 healthy volunteers, phenotyped as either poor or extensive metabolizers of CYP2D6, were enrolled. They received a 160-mg single oral dose after overnight fasting. Poor metabolizers excreted a slightly higher urinary fraction of mirabegron (15.4 ± 4.2%) than extensive metabolizers (11.7 ± 3.0%). T_{max} in both extensive and poor metabolizers was about 2 hours, and the terminal elimination half-life ($t_{1/2}$) was approximately 23–25 hours.

The clinical effects of mirabegron have been well documented. Nitti et al (2011) reported on a phase III multicenter, randomized, double-blind, parallel-group, placebo-controlled trial of mirabegron in North America. They enrolled 1328 patients ≥18 years old with OAB symptoms for ≥3 months. Patients who completed a 2-week, single-blind, placebo run-in and had ≥8 micturitions/24 hours and ≥3 urgency episodes/72 hours (with or without incontinence) during a 3-day micturition diary period, were randomized to receive placebo, or mirabegron 50 or 100 mg once daily for 12 weeks. Coprimary endpoints were change from baseline to final visit (study end) in the mean number of incontinence episodes/24 hours and micturitions/24 hours. Efficacy was assessed according to patient micturition diaries and safety assessments included adverse event (AE) reporting. Patients were randomized and received study drug (placebo, $n = 453$; mirabegron 50 mg, $n = 442$; mirabegron 100 mg, $n = 433$). Mean age was 60.1 years, 74.3% were female, 29.7% had urgency incontinence, 38.1% had mixed stress/urgency incontinence with urgency predominant, and 32.2% had frequency without incontinence. At the final visit, mirabegron 50 and 100 mg showed statistically significant improvements in the coprimary efficacy endpoints and mean volume voided/micturition compared with placebo. Statistically significant benefits were achieved at the first-measured timepoint of week 4. The incidence of AEs was similar across the placebo and mirabegron 50 and 100 mg groups (50.1%, 51.6%, and 46.9%, respectively). The most common (≥3%) AEs in any treatment group were hypertension (6.6%, 6.1%, and 4.9%, respectively), urinary tract infection (1.8%, 2.7%, and 3.7%), headache (2.0%, 3.2%, and 3.0%) and nasopharyngitis (2.9%, 3.4%, and 2.5%).

Otsuki et al (2013) reported on the efficacy and safety of mirabegron in a predominantly male population of OAB patients. In this prospective, nonrandomized, controlled study, patients with at least one episode of urgency per week and scoring at least 2 for urinary urgency in the Overactive Bladder Symptom Score (OABSS) were enrolled. In this study, 52 patients (36 men) with newly diagnosed OAB received mirabegron 50 mg once daily, and 45 (36 men) with OAB refractory to antimuscarinics switched to mirabegron, and another 27 patients (18 men) with newly diagnosed OAB received antimuscarinics and served as controls. Patients on a stable β_1-AR blocker dose for treatment of LUTS were allowed in the study, but those with a PVR greater than 100 mL were excluded. Mirabegron achieved significant improvement in all efficacy outcomes (OABSS and International Prostate Symptom Score [IPSS]). In patients with newly diagnosed OAB, improvements were not significantly different from those achieved by antimuscarinics. Mirabegron was well tolerated and did not significantly change PVRs. However, these encouraging results for mirabegron in treating male OAB should be interpreted with caution in view of the limitations of the study, which included small patient numbers, lack of randomization, and a suboptimal treatment period for the indication.

In a study by Chapple et al (2013) assessing the 12-month safety and efficacy of mirabegron, tolterodine was used as active control. There were no significant differences in efficacy between drugs. However, whether mirabegron has similar efficacy to antimuscarinics awaits direct comparison studies. Mirabegron seems to have definite advantages over the antimuscarinics with respect to adverse events. Dry mouth and constipation are essentially nonexistent in comparison to placebo (Chapple et al, 2014; Cui et al, 2014; Rossanese et al, 2015; Samuelsson et al, 2015; Warren et al, 2016).

D. New Developments

Thiagamoorthy et al (2015) reviewed "novel and putative" β_3-AR agonists for management of OAB, including CL316243, TRK380, AJ9677, and BRL37344. Another agent, vibegron, was claimed to have an overall superior preclinical profile compared to MK0634, which was discontinued because of unacceptable structure-based toxicity in preclinical species (Edmonson et al, 2016). Even if these agents have been reported as being in development, no clinical data have been published, and it may be questioned whether any of them can be regarded as "novel and putative." Phase II and phase III randomized, double-blind, placebo-controlled studies of ritobegron in patients with OAB have been initiated and completed, but the results have not been published, and it seems that the primary efficacy endpoint of the studies was not met. No new clinical trials with ritobegron seem to have been initiated.

Efficacy and safety of solabegron (GW427353) have been reported in a phase II multicenter, randomized, proof-of-concept trial in 258 women with wet OAB. The drug produced a statistically significant difference in percent change from baseline to week 8 in incontinence episodes over 24 hours (primary outcome) when compared with placebo ($p = .025$) and was well tolerated (Ohlstein et al, 2012).

There seem to be a number of β_3-AR agonists in the pipeline, some of which are under development. However, it is uncertain which, if any, will come to market and be available for the management of OAB.

Ion Channels

A. Calcium Channels

There is no doubt that an increase in $[Ca^{2+}]_i$ is a key process required for the activation of contraction in the detrusor myocyte. However, it remains uncertain whether this increase is due to influx from the extracellular space and/or release from intracellular stores. Furthermore, the importance of each mechanism in different species, and with respect to the particular transmitter studied, has not been firmly established (Kajioka et al, 2002).

Theoretically, inhibition of calcium influx by means of calcium antagonists would be an attractive way of inhibiting DO/OAB. However, there have been few clinical studies of the effects of calcium antagonists in patients with DO. Naglie et al (2002) evaluated the efficacy of nimodipine for geriatric urgency incontinence in a randomized, double-blind, placebo-controlled crossover trial, and concluded that this treatment was unsuccessful.

Thus, available information does not suggest that systemic therapy with calcium antagonists is an effective way to treat DO/OAB (Andersson et al, 2013; Andersson and Wein, 2004).

B. Potassium Channels

Potassium channels represent another mechanism to modulate the excitability of the smooth-muscle cells. There are several different types of K^+ channels, and at least two subtypes have been found in the human detrusor: ATP-sensitive K^+ channels (K_{ATP}) and large conductance calcium-activated K^+ channels (BK_{Ca}). Studies on isolated human detrusor muscle and on bladder tissue from several animal species have demonstrated that K^+-channel openers reduce spontaneous contractions as well as contractions induced by carbachol and electrical stimulants. However, the lack of selectivity of presently available K^+-channel blockers for the bladder versus the vasculature has thus far limited the use of these drugs. The first generation of K-channel openers, such as cromakalim and pinacidil, were found to be more potent as inhibitors of vascular smooth muscle than of detrusor muscle (Andersson and Arner, 2004). No effects of cromakalim or pinacidil on the bladder were found in studies on patients with spinal cord lesions or detrusor instability secondary to outflow obstruction. Also, with more recently developed K_{ATP}-channel openers, claimed to have selectivity toward the bladder, negative results have been obtained in an RTC on patients with idiopathic DO (Chapple et al, 2006).

Thus, at present there is no clinical evidence to suggest that K^+-channel openers represent a treatment alternative for DO/OAB (Andersson et al, 2013; Andersson and Wein, 2004).

$P2X_3$ Receptors and $P2X_3$-Receptor Antagonists

During bladder filling the urothelium is stretched and ATP is released from the umbrella cells, thereby activating mechanotransduction pathways via stimulation of purinergic receptors on suburothelial sensory nerves to initiate the voiding reflex and to mediate the sensation of bladder filling and urgency (Burnstock, 2013, 2014). P2X receptors are ligand-gated ion channels, and seven P2X receptor subunits have been identified from molecular studies and characterized functionally and pharmacologically (North and Surprenant, 2000; Gever et al, 2006; Ford and Cockayne, 2011). Sensory nerve fibers expressing P2X3 immunoreactivity have been found projecting into the lamina propria, urothelium, and detrusor smooth muscle (Ford and Cockayne, 2011), where this and several other P2X receptors are functionally expressed (Ford and Cockayne, 2011; Shabir et al, 2013). As mentioned, ATP is released from the urothelium in response to bladder filling (Ferguson et al, 2007; Vlaskovska et al, 2001; Wang et al, 2005a), and studies using an isolated rodent bladder-pelvic nerve preparation have shown that bladder distension leads to increased afferent nerve activity that is mimicked by ATP and/or α,β-meATP (Namasivayam et al, 2009; Vlaskovska et al, 2001; Rong et al, 2002). Intravesical infusion of ATP or α,β-meATP can directly stimulate bladder overactivity in conscious rats, in a manner that is concentration-dependent and sensitive to the ATP receptor antagonist, TNP-ATP (Pandita and Andersson, 2002). Thus, P2X3 and P2X2/3 receptors may be important in sensing volume changes during normal bladder filling, and may participate in lowering the threshold for C-fiber activation under pathophysiological conditions.

Purinergic signaling in the bladder may be changed in different LUT disorders (Burnstock, 2014). Thus, bladder inflammation can sensitize and enhance P2X receptor function on pelvic visceral and hypogastric splanchnic afferents in the lumbosacral and thoracolumbar DRG (Dang et al, 2005). In bladder urothelial cells from patients with bladder pain syndrome/interstitial cystitis (BPS/IC), P2X3 receptor expression appears to be abnormally up-regulated in response to stretch (Sun and Chai, 2004; Sun et al, 2009). An increased density of P2X3 and TRPV1-expressing nerve fibers has been observed in the bladders of patients with neurogenic detrusor overactivity, and following treatment with resiniferatoxin, patients responding to treatment showed diminished levels of both TRPV1 and P2X3 immunoreactivity (Brady et al, 2004).

P2X receptors, particularly P2X3 receptors, have been of interest for treatment of LUT disorders for a long time (Ford et al, 2006; Ford and Cockayne, 2011; Ford, 2012; North and Jarvis, 2013). Selective P2X3 antagonists, such as A317491, were shown to effectively reduce the signs of cyclophosphamide-induced cystitis (Ito et al, 2008), and to improve bladder function in a rat spinal cord injury (SCI) model (Lu et al, 2007). A317491 produced a dose-dependent inhibition of nonmicturition contractions, increased intermicturition intervals, and bladder capacity, without influencing the amplitude of voiding contractions. Munoz et al (2012) showed that SCI rats had significantly higher frequencies for field potentials and nonvoiding contractions than normal rats. Intravesical ATP increased field potential frequency in control but not SCI rats, while systemic administration of the P2X3/P2X2/3 antagonist, AF353 (Gever et al, 2010), significantly reduced this parameter in both groups. AF353 also reduced the inter-contractile interval in control but not in SCI rats; however, the frequency of nonvoiding contractions in SCI rats was significantly reduced. AF353 was also studied in a closed cystometric model ("refill VIBC") in a urethane-anesthetized rat model. A dose-dependent increase in volume threshold by up to 50–70%, with slightly reduced frequency, but no appreciable change in amplitude, was demonstrated (Ford and Cockayne, 2011). As AF353 penetrates the blood–brain barrier (Gever et al, 2010), it was not clear whether these effects resulted from P2X3 antagonism at peripheral terminals within the bladder wall, or alternatively at central terminals in the spinal cord dorsal horn. It has been suggested that ATP can be released and act on spinal P2X3 and P2X2/3 receptors to affect afferent signals originating from the bladder (Ford, 2012). Spinal ATP may then constitute an endogenous central presynaptic purinergic mechanism to regulate visceral sensory transmission. Further characterization of this spinal purinergic control in visceral activities may help the development of P2X3 and P2X2/3 antagonists to treat urological dysfunction, such as overactive bladder (Ford, 2012).

TRP Channels and TRP Channel Antagonists

The transient receptor potential (TRP) channel superfamily has been shown to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder, and may act as sensors of stretch and/or chemical irritation (Araki et al, 2008; Everaerts et al, 2008; Andersson et al, 2010; Skryma et al, 2011; Avelino et al, 2013; Deruyver et al, 2014; Franken et al, 2014). TRPV1 and TRPV4 channels have been found to be expressed in the urinary bladder (Tominaga et al, 1998; Birder et al, 2001; Gevaert et al, 2007). TRPV1 is present and active both in the urothelium and in the nerve fibers of several species, including humans (Ji et al, 2002; Charrua et al, 2009a). TRPV4 was initially described in the urothelium of rodents and humans (Janssen et al, 2011). Coexpression of the two receptors was observed in 20% of rat urothelial cells (Kullmann et al, 2009). Recent observations indicate, however, that TRPV4 may also be expressed in bladder afferents. In fact, about 30% of L6 dorsal root ganglia neurons that project to the urinary bladder coexpress TRPV1 and TRPV4 (Cao et al, 2009; Charrua et al, 2012a). The physiological meaning of this observation is unclear.

TRPV1 knockout (KO) mice have a normal or quasi-normal phenotype. In awake animals, the only change detected in TRPV1 KO mice was a smaller volume per void when compared with wild-type (WT) controls (Birder et al, 2001). In cystometries performed under anesthesia, the TRPV1 KO mice phenotype seems also very benign. Some studies reported that this animals have totally normal cystometric traces (Charrua et al, 2007). However, other studies showed that TRPV1 KO mice develop a few nonvoiding contractions preceding the voiding contraction (Birder et al, 2001; Frias et al, 2012). Accordingly, TRPV1 antagonists (GRC6211) did not show any relevant effect on bladder activity of intact rodents (Charrua et al, 2009b). In contrast with TRPV1 KO mice, the micturition phenotype of TRPV4 KO animals is clearly abnormal. TRPV4 KO mice are incontinent, most probably due to incomplete bladder emptying (Gevaert et al, 2007) Cystometric studies carried out under physiological conditions revealed that TRPV4 KO mice have an marked increase in the inter-contraction interval when compared to WT littermates (Gevaert et al, 2007; Birder et al, 2002). Likewise, TRPV4 antagonists (HC067047) decreased the frequency of bladder contractions and increased the inter-contraction interval (Everaerts et al, 2010). These observations indicated that TRPV4 has a role in the control of normal micturition reflex.

Indisputably, TRPV1 or TRPV4 play a role in the increase of micturition frequency associated with cystitis (Charrua et al, 2007; Everaerts et al, 2010). While inflamed WT mice exhibit bladder hyperactivity and intense spinal Fos expression after different forms of bladder inflammation, including acetic acid or bacterial extracts, TRPV1 KO mice have normal cystometries and normal spinal c-fos expression (Charrua et al, 2007). The same holds true for TRPV4. In fact, TRPV4 KO mice exhibit significantly lower voiding frequencies and larger voided volumes than WT after inflammation with cyclophosphamide (Everaerts et al, 2010).

The blockade of TRPV1 and TRPV4 with specific antagonist confirm the observations carried out in knockout animals. In fact, the TRPV1 antagonist GRC6211 or the TRPV4 antagonist HC067047 both abolish the increase of micturition frequency associated with chemical cystitis (Everaerts et al, 2010; Charrua et al, 2009b). Recently, it was shown that the systemic coadministration of TRPV1 and TRPV4 antagonist was more effective in treating the cystitis-induced increase of micturition frequency than the individual application of each antagonist (Charrua et al, 2012b). The effect could be observed at very low doses of the TRPV1 and TRPV4 antagonists, which had no effect when given isolated. This observed effect might be the answer to overcome the eventual adverse events related with the application of some of these antagonists (Planells-Cases et al, 2011). Just to mention a few, TRPV1 antagonists are associated with hyperthermia and increased risk of cardiac ischemia (Avelino et al, 2012) while TRPV4 antagonists may eventually precipitate urinary retention and overflow incontinence (Gevaert et al, 2007).

It has been known for a long time that TRPV1 is involved in the emergence of neurogenic detrusor overactivity following spinal cord transaction (Avelino and Cruz, 2006). A TRPV1 antagonist, GRC6211, has been shown to decrease reflex detrusor overactivity in rats after chronic spinal cord transaction. With increasing doses, it was possible to obtain a total suppression of bladder activity (Santos-Silva et al, 2012). Kitagawa et al (2013) evaluated the effects of the selective TRPV1 antagonist JTS653 evaluated the effects of JTS653 on the increased pelvic nerve discharge and intravesical pressure induced by intravesical infusion of capsaicin, in anesthetized rats. The drug significantly suppressed both parameters. The clinical relevance of this finding will be certainly further investigated in the future. Interestingly, Uvin et al (2015) found evidence for involvement of TRPM8 in rat and mouse models of acute cold-induced urinary urgency.

There seem to be several links between activation of different members of the TRP superfamily and LUTS/DO/OAB, and further exploration of the involvement these channels in LUT function, normally and in dysfunction, may be rewarding. However, proof of concept studies in humans are still lacking.

Botulinum Toxin–Sensitive Mechanisms

Botulinum toxin (BonT), the neurotoxin produced by *Clostridium botulinum*, comprises seven subtypes, of which subtype A (BONT-A), which has the longest duration of action, is clinically the most relevant. BoNT/A is available in three different commercial forms, which differ in their relative potency: onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A. Although there are differences in potency between the forms, there are no reasons to believe that their basic mechanisms of action are different. Most of the information available preclinically and clinically derives from the use of onabotulinum toxin A.

The mechanisms of action of BoNT in the nerve terminal have been discussed by several investigators (Humeau et al, 2000; Chancellor et al, 2008). Briefly, it involves cleavage of the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment proteins (the SNARE complex) include synaptosome-associated protein 25 kD (SNAP25), synaptobrevin (vesicle associated membrane protein) and syntaxin. BonT/A cleaves SNAP25, rendering the SNARE complex inactive (Humeau et al, 2000; Chancellor et al, 2008). In striated muscle, paralysis occurs and is produced by inhibition of acetylcholine (ACh) release from cholinergic motor nerve endings (Humeau et al, 2000).

In the human bladder, SNAP25 expression has been demonstrated in parasympathetic, sympathetic, and sensory fibers (Coelho et al, 2012). Blockade of ACh release is believed to play an essential role in the detrusor hypo- or acontractility that follows BoNT/A injection in the bladder. Supporting this view, in normal or SCI animals BoNT/A treatment decreased the bladder contractions evoked by electrical stimulation of spinal nerves without altering autonomous contractile activity. However, BoNT/A may also have effects on sensory fibers, since about half of the peptidergic sensory fibers express SNAP25 (Coelho et al, 2012). It has been well documented that BoNT/A can inhibit release from sensory nerves both in the CNS and peripherally (Aoki, 2005; Ikeda et al, 2012; 2006; Lucioni et al, 2008; Meng et al, 2007; Rapp et al, 2006). BoNT/A was found to reduce afferent firing from bladder afferents and antidromic release of neuropeptides (Ikeda et al, 2012).

Although SNAP25 immunoreactivity has not been detected in urothelial cells (Coelho et al, 2012), urothelial function also seems to be compromised after BoNT/A administration. BonT/A has been shown to inhibit ATP release from urothelium in animal models of spinal cord injury (Khera et al, 2004; Smith et al, 2008).

In addition to its effect on neurotransmitter release, BoNT/A, injected into the bladder wall, seems to influence the receptor profile of important neurotransmitters. Apostolidis et al (2005) found that the mucosal levels of P2X3 and TRVP1 were decreased 4 weeks after BoNT/A injection, and even more so after 16 weeks. The decrease in the levels of these receptors seemed to correlate with those patients who experienced decreased urgency after the injection. Datta et al (2010) found that patients with OAB had decreased levels of muscarinic receptors in the urothelium/suburothelium and that the levels of muscarinic receptors 1 and 3 were normalized after treatment with BoNT/A. Furthermore, they found an inverse association with receptor level and patient reported symptoms. The relationship between mucosal receptor profile and patient symptoms indicates that this may be an important effect mechanism of BoNT/A.

Available evidence thus suggests that BoNT/A, by action on both the motor part of the myogenic (release of contractant transmitters) and on the mucosal (release of sensory transmitters) activation pathways, decreases the afferent nervous activity generated by the bladder during filling.

Several RCTs have documented the clinical effects of BoNT/A in both neurogenic and idiopathic DO (Mangera et al, 2011), where the drug decreases incontinence episodes, frequency, and urgency and improves quality of life (Andersson et al, 2013; Sahai et al, 2007; Brubaker et al, 2008; Tincello et al, 2012). However, successful OAB treatment with BoNT/A does not appear to be related to the existence of DO. No differences in outcome were found between those with and those without baseline DO (Kanagarajah et al, 2012; Rovner et al, 2011). BoNT/A is also effective in patients with the OAB syndrome not responding to antimuscarinic drugs (Kanagarajah et al, 2012; Rovner et al, 2011).

The major adverse effects are urinary retention, sometimes requiring clean intermittent catherization, and urinary tract infections. Beneficial effects were shown to not be dose-dependent, while side effects may be lessened at lower doses (Dmochowski et al, 2010).

SUMMARY AND FUTURE ASPECTS

To effectively control bladder activity, and to treat urinary incontinence, identification of suitable targets for pharmacological intervention is necessary. Such targets may be found within or outside the CNS. LUTSs, including OAB/DO, are all conditions that can have major effects on quality of life and social functioning. Antimuscarinic drugs are still first-line pharmacological treatment—they often have good initial response rates, but adverse effects and decreasing efficacy cause long-term compliance problems. β_3-AR antagonists (mirabegron) is an alternative first-line pharmacological treatment with a profile for fewer adverse effects than antimuscarinics. The TRP channel superfamily has been demonstrated to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder and may act as sensors of stretch and/or chemical irritation. However, the roles of these individual receptors for normal LUT function and in LUTS/DO/OAB have not been established. There may be several other new possibilities to treat LUTS/OAB/DO.

There is currently increasing interest in drugs modulating the micturition reflex by a central action. However, central nervous mechanisms have so far not been preferred targets for drugs intended to treat OAB, since selective actions may be difficult to obtain. Drugs with a central mode of action such as NK1 receptor antagonists, tramadol, and gabapentin have positive proof of concept documented in RCTs. Even if neither of these drugs can be recommended for general use in the treatment of LUTS/OAB/DO, they illustrate that agents with a target in the CNS can be therapeutically useful. Thus, even if antimuscarinic drugs and β_3-AR antagonists (mirabegron) provide first-line treatment of the OAB, and their favorable efficacy/tolerability–safety ratio has been confirmed, new drugs are needed.

BIBLIOGRAPHY

Abrams P, Andersson KE: Muscarinic receptor antagonists for overactive bladder. BJU Int 2007;100(5):987–1006.

Abrams P, Cardozo L, Fall M, et al: Standardisation Subcommittee of the International Continence Society. The standardisation of terminology of lower urinary tract function: Report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002;21(2):167–178.

Andersson KE: Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev 1993;45:253.

Andersson KE: Pathways for relaxation of detrusor smooth muscle. Adv Exp Med Biol 1999;462:241–252.

Andersson KE: Bladder activation: Afferent mechanisms. Urology 2002;59(5 Suppl 1):43.

Andersson KE: Antimuscarinics for treatment of overactive bladder. Lancet Neurol 2004a;3(1):46–53.

Andersson KE: Mechanisms of disease: Central nervous system involvement in overactive bladder syndrome. Nat Clin Pract Urol 2004b;1(2):103–108.

Andersson KE: Muscarinic acetylcholine receptors in the urinary tract. Handb Exp Pharmacol 2011;(202):319–344.

Andersson KE: Potential future pharmacological treatment of bladder dysfunction. Basic Clin Pharmacol Toxicol 2016;119(Suppl 3): 75–85.

Andersson KE, Chapple CR, Cardozo L, et al: Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo, Khoury S, Wein A (eds): Incontinence, Proceedings of 5th International Consultation on Incontinence (ICUD-EAU), 2013, pp 623–728.

Andersson KE, Arner A: Urinary bladder contraction and relaxation: Physiology and pathophysiology. Physiol Rev 2004;84(3):935–986.

Andersson KE, Campeau L, Olshansky B: Cardiac effects of muscarinic receptor antagonists used for voiding dysfunction. Br J Clin Pharmacol 2011;72(2):186–196.

Andersson KE, Gratzke C: Pharmacology of alpha1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nat Clin Pract Urol 2007;4(7):368–378.

Andersson KE, Gratzke C, Hedlund P: The role of the transient receptor potential (TRP) superfamily of cation-selective channels in the management of the overactive bladder. BJU Int 2010;106(8):1114–1127.

Andersson KE, Pehrson R: CNS involvement in overactive bladder: Pathophysiology and opportunities for pharmacological intervention. Drugs 2003;63(23):2595–2611.

Andersson KE, Wein AJ: Pharmacology of the lower urinary tract: Basis for current and future treatments of urinary incontinence. Pharmacol Rev 2004;56(4):581–631.

Andersson KE, Yoshida M: Antimuscarinics and the overactive detrusor—which is the main mechanism of action? Eur Urol 2003;43(1):1–5.

Aoki KR: Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology 2005;26: 785–793.

Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006;49(4):644–650.

Apostolidis A, Popta R, Yiangou Y, et al: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005;174:977–982; discussion 982–983.

Araki I, Du S, Kobayashi H, et al: Roles of mechanosensitive ion channels in bladder sensory transduction and overactive bladder. Int J Urol 2008;15(8):681–687.

Avelino A et al: Transient receptor potential channels in bladder function. Acta Physiol (Oxford). 2013;207(1):110–122.

Avelino A, Cruz F: TRPV1 (vanilloid receptor) in the urinary tract: expression, function and clinical applications. Naunyn Schmiedebergs Arch Pharmacol 2006;373(4):287–299.

Bechis SK, Kim MM, Wintner A, Kreydin EI: Differential response to medical therapy for male lower urinary tract symptoms. Curr Bladder Dysfunct Rep 2015;10:177–185.

Birder L, Andersson KE: Urothelial signaling. Physiol Rev 2013;93(2):653–680.

Birder LA, Kanai AJ, de Groat WC, et al: Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. Proc Natl Acad Sci USA 2001;98(23):13396–13401.

Birder LA, Nakamura Y, Kiss S, et al: Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 2002;5(9):856–860.

Birder LA, de Groat WC: Mechanisms of disease: Involvement of the urothelium in bladder dysfunction. Nat Clin Pract Urol 2007;4(1):46–54.

Blok BF, de Weerd H, Holstege G: The pontine micturition center projects to sacral cord GABA immunoreactive neurons in the cat. Neurosci Lett 1997;233(2–3):109–112.

Bouchelouche K, Andersen L, Alvarez S, et al: Increased contractile response to phenylephrine in detrusor of patients with bladder outlet obstruction: Effect of the alpha1A and alpha1D-adrenergic receptor antagonist tamsulosin. J Urol 2005;173(2):657–661.

Brading AF, McCloskey KD: Mechanism of disease: Specialized interstitial cells of the urinary tract-an assessment of current knowledge. Nat Clin Pract Urol 2005;11:546–554.

Brady CM, Apostolidis A, Yiangou Y, et al: P2X3-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin. Eur Urol 2004;46(2):247–253.

Braverman AS, Tallarida RJ, Ruggieri MR Sr: Interaction between muscarinic receptor subtype signal transduction pathways mediating bladder contraction. Am J Physiol Regul Integr Compar Physiol 2002;283(3):R663–R668.

Braverman AS, Ruggieri MR Sr. Hypertrophy changes the muscarinic receptor subtype mediating bladder contraction from M3 toward M2. Am J Physiol Regul Integr Compar Physiol 2003;285(3):R70 1–R708.

Brubaker L, Richter HE, Visco A, et al: Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol 2008;180:217–222.

Bschleipfer T, Schukowski K, Weidner W, et al: Expression and distribution of cholinergic receptors in the human urothelium. Life Sci 2007;80(24–25):2303–2307.

Burnstock G: Purinergic signalling in the urinary tract in health and disease. Purinerg Signal 2014;10(1):103–155.

Burnstock G: Purinergic signalling in the lower urinary tract. Acta Physiol (Oxford) 2013;207(1):40–52.

Candenas L, Lecci A, Pinto FM, et al: Tachykinins and tachykinin receptors: Effects in the genitourinary tract. Life Sci 2005;76(8):835–862.

Cao DS, Yu SQ, Premkumar LS: Modulation of transient receptor potential Vanilloid 4-mediated membrane currents and synaptic transmission by protein kinase C Mol Pain 2009;5:5.

Carbone A, Palleschi G, Conte A, et al: The effect of gabapentin on neurogenic detrusor over-activity, a pilot study. Eur Urol 2003;2(Suppl):141 (abstract 555).

Chancellor MB, Fowler CJ, Apostolidis A, et al: Drug insight: Biological effects of botulinum toxin A in the lower urinary tract. Nat Clin Pract Urol 2008;5:319–328.

Chapple C, Khullar V, Gabriel Z, et al: The effects of antimuscarinic treatments in overactive bladder: A systematic review and meta-analysis. Eur Urol 2005;48:5–26.

Chapple CR, Patroneva A, Raines SR. Effect of an ATP-sensitive potassium channel opener in subjects with overactive bladder: A randomized, double-blind, placebo-controlled study (ZD0947IL/0004). Eur Urol 2006;49:879–886.

Chapple CR, Khullar V, Gabriel Z, et al: The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. Eur Urol 2008;54(3):543.

Chapple CR, Kaplan SA, Mitcheson D, et al: Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. Eur Urol 2013;63(2):296–305.

Chapple CR et al: Mirabegron in overactive bladder: A review of efficacy, safety, and tolerability. Neurourol Urodyn 2014;33(1):17–30.

Charrua A, Cruz CD, Cruz F, Avelino A: Transient receptor potential vanilloid subfamily 1 is essential for the generation of noxious bladder input and bladder overactivity in cystitis. J Urol 2007;177(4):1537–1541.

Charrua A, Cruz CD, Narayanan S, et al: GRC-6211, a new oral specific TRPV1 antagonist, decreases bladder overactivity and noxious bladder input in cystitis animal models. J Urol 2009b;181(1):379–386.

Charrua A, Reguenga C, Cordeiro JM, et al: Functional transient receptor potential vanilloid 1 is expressed in human urothelial cells. J Urol 2009a;182(6):2944–2950.

Charrua A, Boudes M, de Ridder D, et al: TRPV1 and TRPV4 expression in bladder neurons during normal condition and during cystitis. Eur Urol Suppl 2012a;11(1):e366.

Charrua A, Cruz CD, Cruz F: TRPV1 and TRPV4 antagonist have synergistic effect for treating bladder overactivity in rats. Eur Urol Suppl 2012b;11(1):e366.

Chebib M, Johnston GAR: The “ABC” of GABA receptors: A brief review. Clin Exp Pharmacol Physiol 1999;26(11):937–940.

Chen Q, Takahashi S, Zhong S, et al: Function of the lower urinary tract in mice lacking 1D-adrenoceptor. J Urol 2005;174(1):370–374.

Chess-Williams R: Muscarinic receptors of the urinary bladder: Detrusor, urothelial and prejunctional. Auton Autacoid Pharmacol 2002;22(3):133–145.

Cockayne DA, Hamilton SG, Zhu QM, et al: Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. Nature 2000;407(6807):1011–1015.

Coelho A, Cruz F, Cruz CD, Avelino A: Spread of onabotulinumtoxinA after bladder injection. Experimental study using the distribution of cleaved SNAP-25 as the marker of the toxin action. Eur Urol 2012;61:1178–1184.

Covenas R, Martin F, Belda M, et al: Mapping of neurokinin-like immunoreactivity in the human brainstem. BMC Neurosci 2003;4(1):3.

Cruz F, Silva C: Botulinum toxin in the management of lower urinary tract dysfunction: Contemporary update. Curr Opin Urol 2004;14(6):329–334.

Cui Y, Zong H, Yang C, Yan H, Zhang Y: The efficacy and safety of mirabegron in treating OAB: A systematic review and meta-analysis of phase III trials. Int Urol Nephrol 2014;46(1):275–284.

D’Agostino G, Condino AM: Involvement of β-adrenoceptors in the inhibitory control 3 of cholinergic activity in human bladder: Direct evidence by [^{3}H]-acetylcholine release experiments in the isolated detrusor. Eur J Pharmacol 2015;758:115–122.

Dang K, Lamb K, Cohen M, Bielefeldt K, Gebhart GF: Cyclophosphamide-induced bladder inflammation sensitizes and enhances P2X receptor function in rat bladder sensory neurons. J Neurophysiol 2008;99(1):49–59.

Das AK, Leggett RE, Whitbeck C, et al: Effect of doxazosin on rat urinary bladder function after partial outlet obstruction. Neurourol Urodyn 2002;21(2):160–166.

Datta SN, Roosen A, Oullen A, et al: Immunohistochemical expression of muscarinic receptors in the urothelium and suburothelium of neurogenic and idiopathic overactive human bladders, and changes with botulinum neurotoxin administration. J Urol 2010;184:2578–2585.

de Groat WC: Influence of central serotonergic mechanisms on lower urinary tract function. Urology 2002;59(5 Suppl 1):30–36.

de Groat WC: The urothelium in overactive bladder: Passive bystander or active participant? Urology 2004;64(6 Suppl 1):7–11.

de Groat WC: Integrative control of the lower urinary tract: Preclinical perspective. Br J Pharmacol 2006;147(Suppl 2):S25–S40.

de Groat WC, Yoshimura N: Pharmacology of the lower urinary tract. Annu Rev Pharmacol Toxicol 2001;41:691–721.

de Groat WC, Yoshimura N: Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Prog Brain Res 2006;152:59–84.

de Groat WC, Yoshimura N: Afferent nerve regulation of bladder function in health and disease. Handb Exp Pharmacol 2009(194):91–138.

de Groat WC, Yoshimura N: Anatomy and physiology of the lower urinary tract. Handb Clin Neurol 2015;130:61–108.

De Laet K, Wyndaele JJ: Adverse events after botulinum A toxin injection for neurogenic voiding disorders. Spinal Cord 2005;43(7):397–399.

Deruyver Y, Voets T, De Ridder D, Everaerts W: Transient receptor potential channel modulators as pharmacological treatments for lower urinary tract symptoms (LUTS): Myth or reality? BJU Int 2015;115(5):686–697.

Dmochowski R, Chapple C, Nitti VW, et al: Efficacy and safety of onabotulinumtoxin A for idiopathic overactive bladder: A double-blind, placebo controlled, randomized, dose ranging trial. J Urol 2010;184:2416–2422.

Edmondson SD, Zhu C, Kar NF, et al: Discovery of Vibegron: A potent and selective β3 adrenergic receptor agonist for the treatment of overactive bladder. J Med Chem 2016;59(2):609–623.

Everaerts W, Gevaert T, Nilius B, De Ridder D: On the origin of bladder sensing: Tr(i)ps in urology. Neurourol Urodyn 2008;27(4):264–273.

Ferguson DR, Kennedy I, Burton TJ: ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes—a possible sensory mechanism? J Physiol 1997;505(Pt 2):503–511.

Ford AP: In pursuit of P2X3 antagonists: Novel therapeutics for chronic pain and afferent sensitization. Purinergic Signal 2012);8(Suppl 1):S3–S26.

Ford AP, Gever JR, Nunn PA, et al: Purinoceptors as therapeutic targets for lower urinary tract dysfunction. Br J Pharmacol 2006;147(Suppl 2):S132.

Ford AP, Cockayne DA: ATP and P2X purinoceptors in urinary tract disorders. Handb Exp Pharmacol 2011;(202):485–526.

Ford AP, Undem BJ: The therapeutic promise of ATP antagonism at P2X3 receptors in respiratory and urological disorders. Front Cell Neurosci 2013;7:267.

Fowler CJ, Griffiths D, de Groat WC: The neural control of micturition. Nat Rev Neurosci 2008;9(6):453–466.

Franken J, Uvin P, De Ridder D, Voets T: TRP channels in lower urinary tract dysfunction. Br J Pharmacol 2014;171(10):2537–2551.

Frazier EP, Peters SLM, Braverman AS, et al: Signal transduction underlying control of urinary bladder smooth muscle tone by muscarinic receptors and β-adrenoceptors. Naunyn-Schmiedeberg’s Arch Pharmacol 2008;377:449.

Frenkl TL, Zhu H, Reiss T, et al: A multicenter, double-blind, randomized, placebo controlled trial of a neurokinin-1 receptor antagonist for overactive bladder. J Urol 2010;184(2):616–622.

Gevaert T, Vriens J, Segal A, et al: Deletion of the transient receptor potential cation channel TRPV4 impairs murine bladder voiding. J Clin Invest 2007;117(11):3453–3462.

Gever JR, Cockayne DA, Dillon MP, Burnstock G, Ford AP: Pharmacology of P2X channels. Pflugers Arch 2006;452(5):513–537.

Gillespie JI, Rouget C, Palea S, et al: Beta adrenergic modulation of spontaneous microcontractions and electrical field-stimulated contractions in isolated strips of rat urinary bladder from normal animals and animals with partial bladder outflow obstruction. Naunyn Schmiedebergs Arch Pharmacol 2015a;388(7):719–726.

Gillespie JI, Rouget C, Palea S, et al: The characteristics of intrinsic complex micro-contractile activity in isolated strips of the rat bladder. Naunyn Schmiedebergs Arch Pharmacol 2015b;388(7):709–718.

Gotoh M, Kamihira O, Kinikawa T, et al: Comparison of α_{1A}-selective adrenoceptor antagonist, tamsulosin, and α_{1D}-selective adrenoceptor antagonist, naftopidil, for efficacy and safety in the treatment of benign prostatic hyperplasia: A randomized controlled trial. BJU Int 2005;96(4):581–586.

Green SA, Alon A, Ianus J, et al: Efficacy and safety of a neurokinin-1 receptor antagonist in postmenopausal women with overactive bladder with urge urinary incontinence. J Urol 2006;176(6 Pt 1): 2535–2540.

Griffiths DJ: Cerebral control of bladder function. Curr Urol Rep 2004;5(5):348–352.

Griffiths D, Derbyshire S, Stenger A, Resnick N: Brain control of normal and overactive bladder. J Urol 2005;174(5):1862–1867.

Guay DR: Clinical pharmacokinetics of drugs used to treat urge incontinence. Clin Pharmacokinet 2003;42(14):1243–1285.

Hampel C, Dolber PC, Smith MP, et al: Modulation of bladder alpha1-adrenergic receptor subtype expression by bladder outlet obstruction. J Urol 2002;167:1513–1521.

Hegde SS, Choppin A, Bonhaus D, et al: Functional role of M-2 and M-3 muscarinic receptors in the urinary bladder of rats in vitro and in vivo. Br J Pharmacol 1997;120:1409–1418.

Herbison P, Hay-Smith J, Ellis G et al: Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: Systematic review. BMJ 2003;326(7394):841–844.

Holstege G: Micturition and the soul. J Compar Neurol 2005;493(1):15–20.

Humeau Y, Doussau F, Grant NJ, Poulain B: How botulinum and tetanus neurotoxins block neurotransmitter release. Biochimie 2000;82:427–446.

Igawa Y, Aizawa N, Homma Y: Beta3-adrenoceptor agonists: Possible role in the treatment of overactive bladder. Korean J Urol 2010;51(12):811–818.

Igawa Y, Michel MC: Pharmacological profile of β3-adrenoceptor agonists in clinical development for the treatment of overactive bladder syndrome. Naunyn Schmiedebergs Arch Pharmacol 2013;386(3):177–183.

Ikeda Y, Zabbarova I, Birder L, et al: Botulinum neurotoxin serotype A suppresses neurotransmitter release from afferent as well as efferent nerves in the urinary bladder. Eur Urol 2012;62(6):1157–1164.

Ikemoto I, Kiyota H, Ohishi Y, et al: Usefulness of tamsulosin hydrochloride and naftopidil in patients with urinary disturbances caused by benign prostatic hyperplasia: A comparative, randomized, two-drug crossover study. Int J Urol 2003;10(11):587–594.

Ji RR, Samad TA, Jin SX, et al: p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. Neuron 2002;36(1):57–68.

Kajioka S, Nakayma S, McMurray G, et al: Ca(2+) channel properties in smooth muscle cells of the urinary bladder from pig and human. Eur J Pharmacol 2002;443(1–3):19–29.

Kanai A, Andersson KE: Bladder afferent signaling: Recent findings. J Urol 2010;183(4):1288–1295.

Kanagarajah P, Ayyathurai R, Caruso DJ, Gomez C, Gousse AE: Role of botulinum toxin-A in refractory idiopathic overactive bladder patients without detrusor overactivity. Int Urol Nephrol 2012;44:91–97.

Katofiasc MA, Nissen J, Audia JE, et al: Comparison of the effects of serotonin selective norepinephrine selective, and dual serotonin and norepinephrine reuptake inhibitors on lower urinary tract function in cats. Life Sci 2002;71(11):1227–1236.

Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP: Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int 2004;45:987–993.

Kim YT, Kwon DD, Kim J, et al: Gabapentin for overactive bladder and nocturia after anticholinergic failure. Int Braz J Urol 2004;30(4):275–278.

Kim Y, Yoshimura N, Masuda H, et al: Antimuscarinic agents exhibit local inhibitory effects on muscarinic receptors in bladder-afferent pathways. Urology 2005;65(2):238–242.

Kitagawa Y, Wada M, Kanehisa T, et al: JTS-653 blocks afferent nerve firing and attenuates bladder overactivity without affecting normal voiding function. J Urol 2013;189(3):1137–1146.

Kuipers R, Mouton LJ, Holstege G: Afferent projections to the pontine micturition center in the cat. J Compar Neurol 2006;494(1):36–53.

Kullmann FA, Shah MA, Birder LA, de Groat WC: Functional TRP and ASIC-like channels in cultured urothelial cells from the rat. Am J Physiol Renal Physiol 2009;296(4):F892–F901.

Lazzeri M, Spinelli M, Zanollo A, Turini D: Intravesical vanilloids and neurogenic incontinence: Ten years experience. Urol Int 2004;72(2):145–149.

Lecci A, Maggi CA: Tachykinins as modulators of the micturition reflex in the central and peripheral nervous system. Regul Pept 2001;101(1–3):1–18.

Lu SH, de Groat WC, Lin AT, Chen KK, Chang LS: Evaluation of purinergic mechanism for the treatment of voiding dysfunction: A study in conscious spinal cord-injured rats. J Chin Med Assoc 2007;70(10):439–444.

Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE: Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int 2008;101:366–370.

Maggi CA, Barbanti G, Santicioli P, et al: Cystometric evidence that capsaicin-sensitive nerves modulate the afferent branch of micturition reflex in humans. J Urol 1989;142(1):150–154.

Malloy BJ, Price DT, Price RR, et al: Alpha1-adrenergic receptor subtypes in human detrusor. J Urol 1998;160:937–943.

Maneuf YP, Gonzalez MI, Sutton KS, et al: Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol Life Sci 2003;60(4):742–750.

Mangera A, Andersson KE, Apostolidis A, et al: Contemporary management of lower urinary tract disease with botulinum toxin A: A systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol 2011;60:784–795.

Mansfield KJ, Liu L, Mitchelson FJ, et al: Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: Changes in ageing. Br J Pharmacol 2005;144(8):1089–1099.

Massaro AM, Lenz KL: Aprepitant: A novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother 2005;39(1):77–85.

McCloskey KD: Interstitial cells in the urinary bladder–localization and function. Neurourol Urodyn 2010;29(1):82–87.

Meng J, Wang J, Lawrence G, Dolly JO: Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. J Cell Sci 2007;120(Pt 16):2864–2874.

Michel MC, Vrydag W: Alpha(1)-, alpha(2)- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol 2006;147(Suppl 2):S88–S119.

Movig KL, Leufkens HG, Belitser SV, et al: Selective serotonin reuptake inhibitor-induced urinary incontinence. Pharmacoepidemiol Drug Saf 2002;11(4):271–279.

Munoz A, Somogyi GT, Boone TB, Ford AP, Smith CP: Modulation of bladder afferent signals in normal and spinal cord-injured rats by purinergic P2X3 and P2X2/3 receptors. BJU Int 2012;110(8 Pt B): E409–E414.

Murakami S, Chapple CR, Akino H, et al: The role of the urothelium in mediating bladder responses to isoprenaline. BJU Int 2007;99(3):669.

Naglie G, Radomski SB, Brymer C, et al: A randomized, double-blind, placebo controlled crossover trial of nimodipine in older persons with detrusor instability and urge incontinence. J Urol 2002;167(2 Pt 1):586–590.

Namasivayam S, Eardley I, Morrison JF: Purinergic sensory neurotransmission in the urinary bladder: An in vitro study in the rat. BJU Int 1999;84(7):854–860.

Nomiya M, Yamaguchi O: A quantitative analysis of mRNA expression of alpha 1 and beta-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. J Urol 2003;170(2 Pt 1):649–653.

North RA, Jarvis MF: P2X receptors as drug targets. Mol Pharmacol 2013;83(4):759–769.

North RA, Surprenant A: Pharmacology of cloned P2X receptors. Annu Rev Pharmacol Toxicol 2000;40:563–580.

Novara G, Galfano A, Secco S, et al: Systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol 2008;54(4):740–763.

Ohlstein EH, von Keitz A, Michel MC: A multicenter, double-blind, randomized, placebo-controlled trial of the β3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol 2012;62(5):834–840.

O'Reilly BA, Kosaka AH, Chang TK, et al: P2X receptors and their role in female idiopathic detrusor instability. J Urol 2002;167(1):157–164.

Otsuka A, Shinbo H, Matsumoto R, et al: Expression and functional role of beta-adrenoceptors in the human urinary bladder urothelium. Naunyn Schmiedebergs Arch Pharmacol 2008;377(4–6):473.

Otsuki H, Kosaka T, Nakamura K, et al: β3-Adrenoceptor agonist mirabegron is effective for overactive bladder that is unresponsive to antimuscarinic treatment or is related to benign prostatic hyperplasia in men. Int Urol Nephrol 2013;45(1):53–60.

Pandita RK, Pehrson R, Christoph, et al: Actions of tramadol on micturition in awake, freely moving rats. Br J Pharmacol 2003;139(4):741–748.

Pandita RK, Andersson KE: Intravesical adenosine triphosphate stimulates the micturition reflex in awake, freely moving rats. J Urol 2002;168(3):1230–1234.

Pehrson R, Andersson KE: Effects of tiagabine, a gamma-aminobutyric acid re-uptake inhibitor, on normal rat bladder function. J Urol 2002;167(5):2241–2246.

Pehrson R, Lehmann A, Andersson KE, et al: Effects of gamma-aminobutyrate B receptor modulation on normal micturition and oxyhemoglobin induced detrusor overactivity in female rats. J Urol 2002;168(6):2700–2705.

Pehrson R, Stenman E, Andersson KE: Effects of tramadol on rat detrusor overactivity induced by experimental cerebral infarction. Eur Urol 2003;44(4):495–499.

Pehrson R, Andersson KE: Tramadol inhibits rat detrusor overactivity caused by dopamine receptor stimulation. J Urol 2003;170(1):272–275.

Persson K, Pandita RK, Spitsbergen JM, et al: Spinal and peripheral mechanisms contributing to hyperactive voiding in spontaneously hypertensive rats. Am J Physiol 1998;275:R1366–R1373.

Planells-Cases R, Valente P, Ferrer-Montiel A, et al: Complex regulation of TRPV1 and related thermo-TRPs: implications for therapeutic intervention. Adv Exp Med Biol 2011;704:491–515.

Pontari MA, Braverman AS, Ruggieri MR Sr: The M2 muscarinic receptor mediates in vitro bladder contractions from patients with neurogenic bladder dysfunction. Am J Physiol Regul Integr Compar Physiol 2004;286(5):R874–R880.

Raffa RB, Friderichs E: The basic science aspect of tramadol hydrochloride. Pain Rev 1996;3:249–271.

Ramage AG: The role of central 5-hydroxytryptamine (5-HT, serotonin) receptors in the control of micturition. Br J Pharmacol 2006;147(Suppl 2):S120–S131.

Rapp DE, Lucioni A, Katz EE, et al: Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: An initial experience. Urology 2004;63(6):1071–1075.

Rapp DE, Turk KW, Bales GT, Cook SP: Botulinum toxin type A inhibits calcitonin gen-related peptide release from isolated rat bladder. J Urol 2006;175:1138–1142.

Reitz A, Schurch B: Intravesical therapy options for neurogenic detrusor overactivity. Spinal Cord 2004;42(5):267–272.

Rekling JC, Funk GD, Bayliss DA, et al: Synaptic control of motoneuronal excitability. Physiol Rev 2000;80(2):767–852.

Roden DM: Drug-induced prolongation of the QT interval. New Engl J Med 2004;350(10):1013–1022.

Rong W, Spyer KM, Burnstock GL: Activation and sensitisation of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. J Physiol 2002;541(Pt 2): 591–600.

Rossanese M, Novara G, Challacombe B, Iannetti A, Dasgupta P, Ficarra V: Critical analysis of phase II and III randomised control trials (RCTs) evaluating efficacy and tolerability of a β3-adrenoceptor agonist (Mirabegron) for overactive bladder (OAB). BJU Int 2015;115(1):32–40.

Rouget C, Rekik M, Camparo P, et al: Modulation of nerve-evoked contractions by β3-adrenoceptor agonism in human and rat isolated urinary bladder. Pharmacol Res 2014;80:14–20.

Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P: Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxin A in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourol Urodyn 2011;30:556–562.

Sacco E, Bientinesi R: Innovative pharmacotherapies for women with overactive bladder: Where are we now and what is in the pipeline? Int Urogynecol J 2015;26:629–640.

Safarinejad MR, Hosseini SY: Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: A double-blind, placebo-controlled, randomized study. Br J Clin Pharma col 2006;61(4):456–463.

Retraction in: Br J Clin Pharmacol 2014;77(1):216.

Saffroy M, Torrens Y, Glowinski J, et al: Autoradiographic distribution of tachykinin NK2 binding sites in the rat brain: Comparison with NK1 and NK3 binding sites. Neuroscience 2003;116(3):761–773.

Sahai A, Kalsi V, Khan, MS, Fowler CJ: Botulinum toxin for the treatment of lower urinary tract symptoms: A review. Neurourol Urodyn 2005;24(1):2–12.

Sahai A, Khan MS, Dasgupta P: Efficacy of botulinum toxin A for treating idiopathic detrusor overactivity: Results from a single center, randomized, double-blind, placebocontrolled trial. J Urol 2007;177:2231–2236.

Samuelsson E et al: Effect of pharmacological treatment for urinary incontinence in the elderly and frail elderly: A systematic review. Geriatr Gerontol Int 2015;15(5):521–534.

Santos-Silva A, Charrua A, Cruz CD, et al: Rat detrusor overactivity induced by chronic spinalization can be abolished by a transient receptor potential vanilloid 1 (TRPV1) antagonist. Auton Neurosci 2012;166(1–2):35–38.

Schneider T, Hein P, Michel MC: Signal transduction underlying carbachol-induced contraction of human urinary bladder. J Pharmacol Exp Ther 2004;309(3):1148–1153.

Schurch B, Corcos J: Botulinum toxin injections for paediatric incontinence. Curr Opin Urol 2005;15(4):264–267.

Shabir S, Cross W, Kirkwood LA, et al: Functional expression of purinergic P2 receptors and transient receptor potential channels by the human urothelium. Am J Physiol Renal Physiol 2013;305(3):F396–F406.

Shefchyk SJ: Spinal cord neural organization controlling the urinary bladder and striated sphincter. Prog Brain Res 2002;137:71–82.

Silva C, Silva J, Ribeiro MJ, et al: Urodynamic effect of intravesical resiniferatoxin in patients with neurogenic detrusor overactivity of spinal origin: Results of a double-blind randomized placebo-controlled trial. Eur Urol 2005;48(4):650–655.

Skryma R, Prevarskaya N, Gkika D, Shuba Y: From urgency to frequency: Facts and controversies of TRPs in the lower urinary tract. Nat Rev Urol 2011;8(11):617–630.

Smith MS, Schambra UB, Wilson KH, et al: Alpha1-adrenergic receptors in human spinal cord: Specific localized expression of mRNA encoding alpha1-adrenergic receptor subtypes at four distinct levels. Brain Res Mol Brain Res 1999;63(2):254–261.

Smith CP, Franks ME, McNeill BK, et al: Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. J Urol 2003;169(5):1896–1900.

Smith CP, Gangiano DA, Munoz A, et al: Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. Neurochem Int 2008;52:1068–1075.

Somogyi GT, Zernova, GV, Yoshiyama M, et al: Change in muscarinic modulation of transmitter release in the rat urinary bladder after spinal cord injury. Neurochem Int 2003;43(1):73–77.

Steers WD, Herschorn S, Kreder KJ, et al: Duloxetine compared with placebo for treating women with symptoms of overactive bladder. BJU Int 2007;100(2):337.

Sugaya K, Ogawa Y, Hatano T, et al: Evidence for involvement of the subcoeruleus nucleus and nucleus raphe magnus in urine storage and penile erection in decerebrate rats. J Urol 1998;159(6):2172–2176.

Sugaya K, Nishijima S, Miyazato M, et al: Effects of intrathecal injection of tamsulosin and naftopidil, alpha-1A and 1D adrenergic receptor antagonists, on bladder activity in rats. Neurosci Lett 2002;328(1):74–76.

Sugaya K Nishijima S, Miyazato M, Ogawa Y: Central nervous control of micturition and urine storage. J Smooth Muscle Res 2005;41(3):117–132.

Sui GP, Rothery, S, Dupont E, et al: Gap junctions and connexin expression in human suburothelial interstitial cells. BJU Int 2002;90(1):118–129.

Sui GP, Wu C, Fry CH: Electrical characteristics of suburothelial cells isolated from the human bladder. J Urol 2004;171(2 Pt 1):938–943.

Sun Y, Chai TC: Up-regulation of P2X3 receptor during stretch of bladder urothelial cells from patients with interstitial cystitis. J Urol 2004;171(1):448–452.

Sun Y, Keay S, Lehrfeld TJ, Chai TC: Changes in adenosine triphosphate-stimulated ATP release suggest association between cytokine and purinergic signaling in bladder urothelial cells. Urology 2009;74(5):1163–1168.

Tai C, Miscik CL, Ungerer TD, et al: Suppression of bladder reflex activity in chronic spinal cord injured cats by activation of serotonin 5-HT(1A) receptors. Exp Neurol 2006;199(2):427–437.

Takahashi R, Nishimura J, Hirano K, et al: Ca^{2+} sensitization in contraction of human bladder smooth muscle. J Urol 2004; 172(2):748–752.

Takusagawa S, van Lier JJ, Suzuki K, Nagata M: Absorption, metabolism and excretion of [14C]Mirabegron (YM178), a potent and selective β3-adrenoceptor agonist, after oral administration to healthy male volunteers. Drug Metab Dispos 2012;40(4):815–824.

Thiagamoorthy G, Giarenis I, Cardozo L: Early investigational β3 adreno-receptor agonists for the management of the overactive bladder syndrome. Expert Opin Investig Drugs 2015;24(10):1299–1306.

Thor KB, Donatucci C: Central nervous system control of the lower urinary tract: New pharmacological approaches to stress urinary incontinence in women. J Urol 2004;172(1):27–33.

Thor KB, de Groat WC: Neural control of the female urethral and anal rhabdosphincter and pelvic floor muscles. Am J Physiol Regul Integr Compar Physiol 2010;299(2):R416–R438.

Thor K, Katofiasc MA: Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. J Pharmacol Exp Ther 1995;274(2):1014–1024.

Tincello DG, Kenyon S, Abrams KR, et al: Botulinum toxin A versus placebo for refractory detrusor overactivity in women: A randomized blinded placebo-controlled trial of 240 women (the RELAX study). Eur Urol 2012;62:507–514.

Tominaga M, Caterina MJ, Malmberg AB, et al: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998;21(3):531–543.

Uvin P, Franken J, Pinto S, et al: Essential role of transient receptor potential M8 (TRPM8) in a model of acute cold-induced urinary urgency. Eur Urol 2015;68(4):655–661.

van Gelderen EM, Li Q, Meijer J, et al: An exploratory comparison of the single dose pharmacokinetics of the beta3-adrenoceptor agonist mirabegron in healthy CYP2D6 poor and extensive metabolizers. Clin Pharmacol Ther 2009;85:S88.

Vlaskovska M, Kasakov L, Rong W, et al: P2X3 knock-out mice reveal a major sensory role for urothelially released ATP. J Neurosci 2001;21(15):5670–5677.

Wang EC, Lee JM, Ruiz WG, Balestreire EM, von Bodungen M, Barrick S, Cockayne DA, Birder LA, Apodaca G: ATP and purinergic receptor-dependent membrane traffic in bladder umbrella cells. Clin Invest 2005;115(9):2412–2422.

Warren K, Burden H, Abrams P: Mirabegron in overactive bladder patients: Efficacy review and update on drug safety. Ther Adv Drug Saf 2016;7(5):204–216.

Yokoyama T, Kumon H, Smith CP, et al: Botulinum toxin treatment of urethral and bladder dysfunction. Acta Med Okayama 2002;56(6):271–277.

Yokoyama O, Yusup A, Miwa Y, et al: Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 2005;174(5):2032–2036.

Yoshimura N, Miyazato M, Kitta T, Yoshikawa S: Central nervous targets for the treatment of bladder dysfunction. Neurourol Urodyn 2014;33(1):59–66.

Yoshiyama M, Yamamoto T, de Groat WC: Role of spinal alpha(1)-adrenergic mechanisms in the control of lower urinary tract in the rat. Brain Res 2000;882(1–2):36–44.

This page intentionally left blank

Neurogenic Bladder

28

Anne M. Suskind, MD, MS, FACS

INTRODUCTION

Neurogenic bladder is a term used to describe lower urinary tract (LUT) dysfunction resulting from a neurologic disease or process. This is not a homogenous term, but rather encompasses any neurologic problem that can affect the bladder. The high prevalence of LUT dysfunction among individuals with neurologic disorders is representative of the complex control of the nervous system on the urinary tract. The level and severity of the neurogenic lesion can manifest as varying, but often predictable, symptoms ranging from disorders of storage to those of voiding dysfunction (Panicker et al, 2015).

Accurate diagnosis and proper management of LUT dysfunction in the neurogenic population consist of two main goals: (1) to preserve the safety of the bladder with low-pressure storage and adequate emptying and (2) to maintain a reasonable quality of life in relationship to the bladder. This chapter serves to discuss the neural control of the LUT in a healthy state, LUT dysfunction associated with various neurologic diagnoses, and the workup and treatment of these disorders.

NEURAL CONTROL OF THE LOWER URINARY TRACT (LUT)

Lower urinary tract (LUT) function represents a complex interplay of autonomic and somatic circuitry with the goal of maintaining a low-pressure bladder during filling and periodic voluntary bladder emptying. Normal neural circuitry allows an individual to voluntarily switch between storage and voiding phases, based on a perceived sense of bladder fullness and an assessment of the social appropriateness of the situation (Panicker et al, 2015).

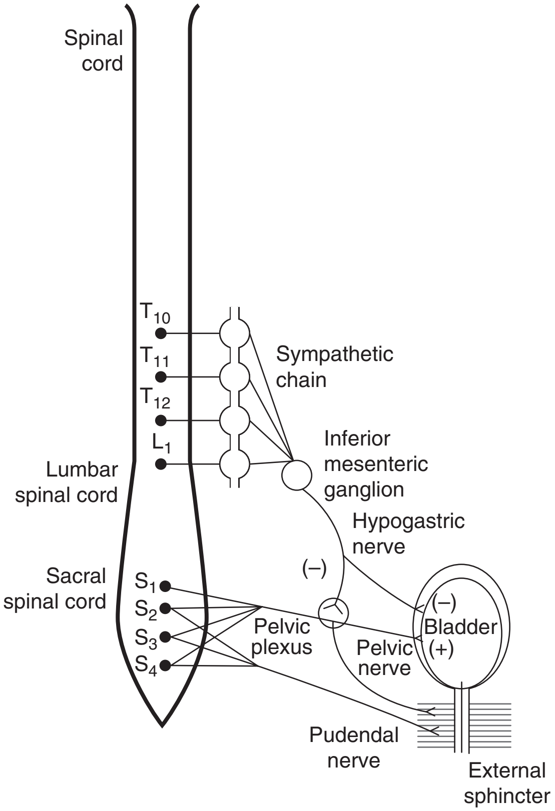
The autonomic nervous system consists of parasympathetic and sympathetic innervation. Sympathetic nerves originate from the thoracolumbar spinal cord segments T10/11 through L2 or L3. These nerves span the lumbar sympathetic ganglion and join the presacral nerve at the superior hypogastric plexus (Figure 28–1). Sympathetic postganglionic nerves release noradrenaline, which activates (1) β-adrenergic receptors, which inhibit the detrusor muscle, causing bladder relaxation; (2) α-adrenergic receptors in the bladder and bladder neck, causing outlet contraction; and (3) β-adrenergic receptors in the bladder ganglia (Andersson and Arner, 2004).

Parasympathetic innervation originates from spinal cord segments S2–S4 as preganglionic nerve fibers that converge into the pelvic nerve. This nerve courses deep in the pelvis on each side of the rectum and terminates at the bladder and urethra. Parasympathetic postganglionic nerves release cholinergic (acetylcholine) and nonadrenergic noncholinergic transmitters. Detrusor contraction can be initiated by release of acetylcholine binding to M_2 and M_3 muscarinic receptors and by noncholinergic transmission mediated by ATP action on P2X purinergic receptors in the bladder muscle. Concurrently, the parasympathetic system releases nitric oxide, which has an inhibitory impact on the urethral smooth muscle (Fowler et al, 2008), further promoting micturition.

The somatic nerve supply to the LUT arises from motor neurons in the anterior horn of S2, S3, and S4 in an area known as **Onuf's nucleus** and reaches the external urethral sphincter via the pudendal nerve (Ghoniem and Hairston, 2005). Somatic cholinergic motor nerves supply the striated external urethral sphincter and are under voluntary control.

During normal bladder filling, sympathetic (hypogastric nerve) and somatic (pudendal nerve) neural mechanisms mediate the contraction of the internal smooth and external striated urethral sphincters, respectively (Figure 28–2A). As the bladder fills, sympathetic-mediated inhibition of the detrusor allows for the bladder to accommodate increasing volumes at low intravesical pressures (Fowler et al, 2008).

When an individual decides that it is time to urinate, the pontine micturition center (PMC) is released from tonic inhibitory control of the higher cortical and subcortical centers of the brain, initiating the voiding process. The



▲ **Figure 28–1.** Neural circuitry responsible for micturition. (Reproduced with permission from Corcos J, Ginsberg D, Karsenty G: Textbook of the Neurogenic Bladder, 3rd ed. New York, NY: CRC Press; 2015.)

parasympathetic system then switches "on," stimulating a detrusor contraction and relaxation of the pelvic floor and external and internal urethral sphincters (Figure 28–2B) (Panicker et al, 2015).

Studies using functional magnetic resonance imaging (fMRI) have further elucidated the process of central nervous system (CNS) control over the LUT and have demonstrated that the periaqueductal gray (PAG) occupies a pivotal role in the switching of circuitry between storage and voiding phases. Frontal, midcingulate, and subcortical areas of the brain all contribute as separate levels of control over the PAG and regulation of the LUT (de Groat et al, 2015). When one or more of these circuits is damaged, LUT dysfunction can occur.

NERVOUS SYSTEM DAMAGE AND LUT DYSFUNCTION

The level and extent of damage to the nervous system often correlates with patterns of LUT dysfunction (Figure 28–3). Damage to the suprasacral and suprapontine nervous systems each results in signs of detrusor overactivity (which can be demonstrated on urodynamics) and symptoms of varying degrees of overactive bladder (urinary urgency, frequency, urgency urinary incontinence, and nocturia). While the signs and symptoms may be similar between both types of neurologic lesions, the underlying pathophysiology behind these symptoms differs. In cases of damage to the suprapontine regions, there is a lack of inhibitory control on the PMC, causing spontaneous and involuntary detrusor contractions. In cases of suprasacral spinal cord lesions, on the contrary, the same symptoms are caused by the emergence of a segmental reflex at the level of the spinal cord that arises after a period of spinal shock.

Suprasacral spinal cord lesions are also noted to have a loss of coordination between the bladder and the sphincter during voiding, resulting in detrusor sphincter dyssynergia (DSD). In DSD, instead of relaxing, the urethral sphincter contracts during voiding, resulting in incomplete bladder emptying and potentially dangerously high bladder pressures during voiding.

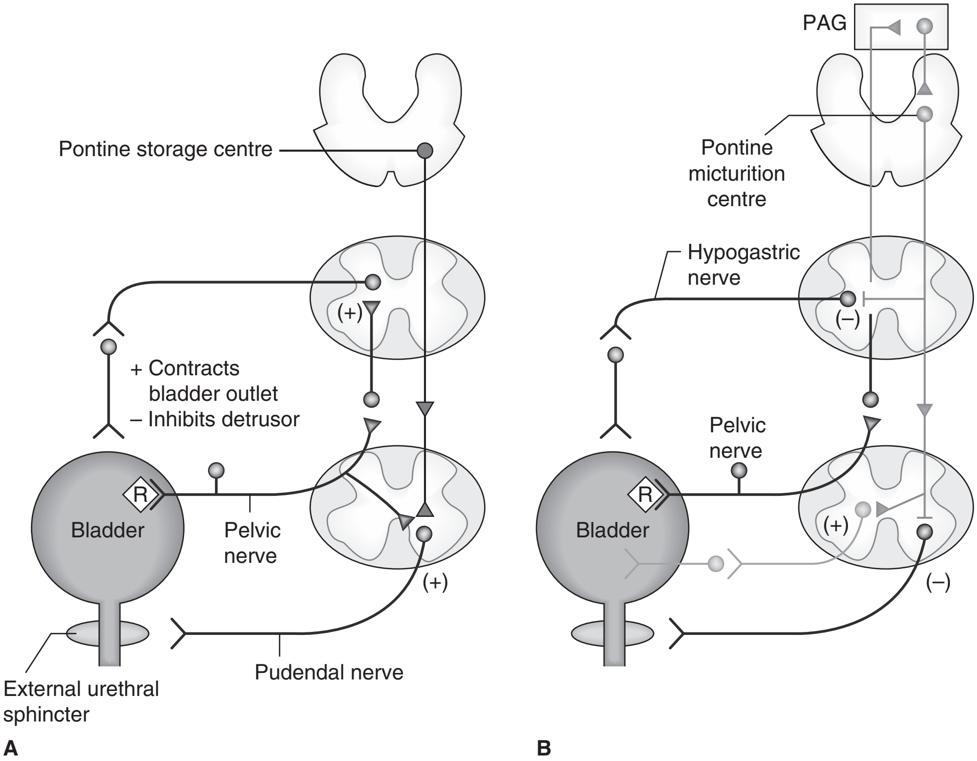
Unlike lesions of the suprapontine and suprasacral nervous system, lesions of the sacral nervous system result in the opposite findings of detrusor hypo- or acontractility. These findings can cause poor or incomplete bladder emptying. There may also be associated poor relaxation of the urethral sphincter (Panicker et al, 2015).

▶ Cerebrovascular Accident

Cerebrovascular accidents, or stroke, are one of the most common causes of death and disability in the United States. Over 50% of individuals with a stroke have some sort of LUT dysfunction. During the acute phase after the cerebrovascular accident, the LUT presents as urinary retention from detrusor areflexia. After resolution of this phase, detrusor overactivity, usually with intact sensation, takes over. These symptoms can also result in urgency urinary incontinence (Panicker et al, 2015; de Groat et al, 2015).

▶ Dementia

Dementia involves atrophy and loss of both gray and white matter of the brain, predominantly in the frontal lobes, which are associated with memory and performing tasks related to mentation. Alzheimer disease is one of the most common forms of dementia in the older population; however, dementia can be difficult to categorize and distinguish from other disorders among this age group. Urinary incontinence tends to be the most common form of LUT dysfunction among this population; however, it can be difficult to determine whether an individual with these symptoms has lost awareness of the desire to voluntarily void or whether there is underlying detrusor overactivity (Panicker et al, 2015; de Groat et al, 2015).



▲ **Figure 28–2.** Neural circuits of storage ***(A)*** and voiding ***(B)*** phases of micturition. (Reproduced with permission from Fowler CJ, Griffiths D, de Groat WC: The neural control of micturition. Nature reviews. Neuroscience Jun 2008;9(6):453–466.)

Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disorder that affects the dopaminergic neurons primarily of the substantia nigra. The major signs of PD include tremor, skeletal rigidity, and bradykinesia. LUT dysfunction, most commonly in the form of overactive bladder symptoms, occurs in anywhere from 50% to 70% of patients with PD (de Groat et al, 2015; Araki et al, 2000). In addition to detrusor overactivity, individuals with PD can also have increased bladder sensation, detrusor underactivity, DSD, and bladder outlet obstruction (Uchiyama et al, 2011), manifest by urinary hesitancy, straining to void, and diminished flow. These symptoms can be attributed to sphincter bradykinesia or, more commonly, to benign prostatic hypertrophy (BPH) (Thavaseelan and Hamid, 2016).

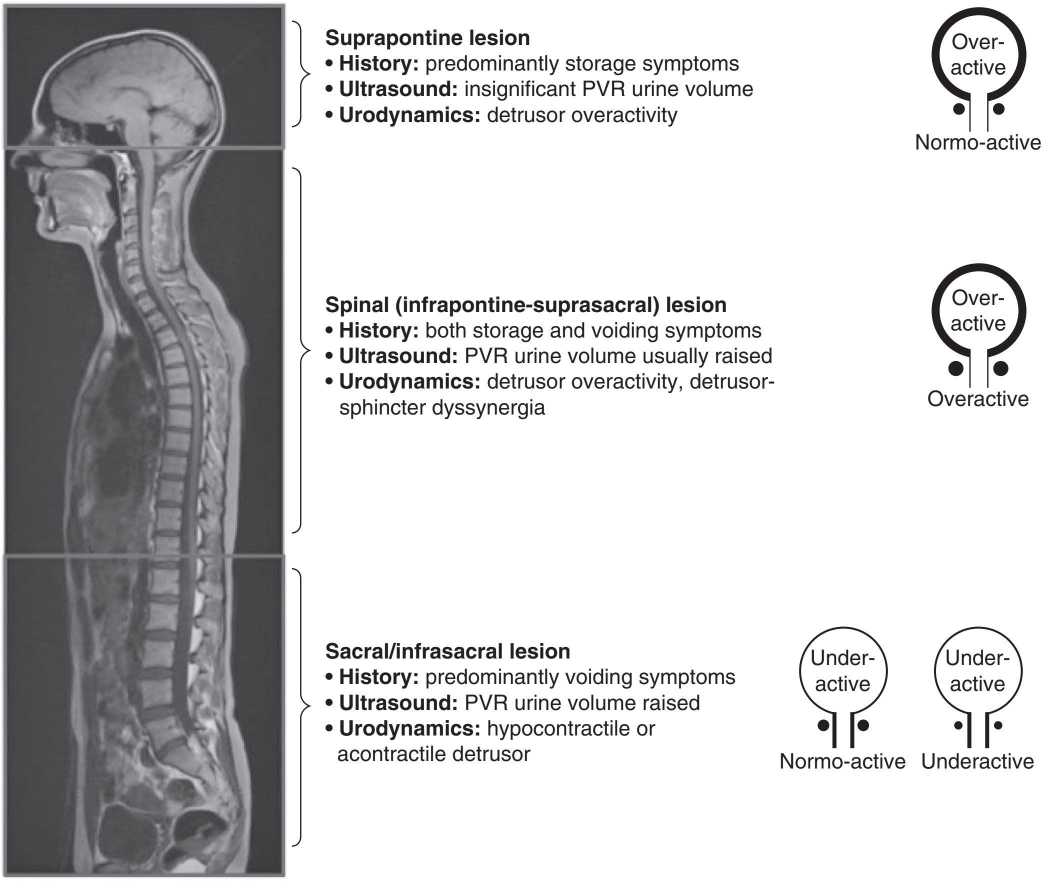
Multiple System Atrophy

Multiple system atrophy (MSA), also known as **Shy–Drager syndrome**, is a progressive neurodegenerative disease of unknown origin. Individuals with MSA exhibit signs of Parkinsonism in addition to cerebellar, autonomic (including urinary and erectile dysfunction), and pyramidal cortical dysfunction. Neurologic lesions associated with MSA are often more severe than those with PD, predisposing individuals to earlier manifestations of more bothersome urinary symptoms. Individuals typically present with urinary urgency, frequency, and urgency urinary incontinence up to 4 years before a diagnosis of MSA is made. The most common LUT finding is detrusor overactivity; however, individuals can also have decreased bladder compliance, difficulty initiating and maintaining voiding, and an open bladder neck (Wein and Dmochowki et al, 2016).

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that typically presents between ages 30 to 38 years and can be classified as relapsing, remitting, or progressive. Female gender predominates with a ratio of 2.3 to 1 (Alonso and Hernan, 2008). Individuals with MS can have symptoms including optic nerve dysfunction, pyramidal tract abnormalities, ataxia, bowel dysfunction, LUT dysfunction, and sexual dysfunction. Lesions can present anywhere in the brain or spinal cord, making LUT symptoms quite variable.

Approximately 10% of individuals with MS present with LUT symptoms, and over 80% develop LUT symptoms at some point during the disease process (Nortvedt et al, 2007).


Suprapontine lesion
• History: predominantly storage symptoms
• Ultrasound: insignificant PVR urine volume
• Urodynamics: detrusor overactivity
Over-active
Normo-active
Spinal (infrapontine-suprasacral) lesion
• History: both storage and voiding symptoms
• Ultrasound: PVR urine volume usually raised
• Urodynamics: detrusor overactivity, detrusor-sphincter dyssynergia
Over-active
Overactive
Sacral/infrasacral lesion
• History: predominantly voiding symptoms
• Ultrasound: PVR urine volume raised
• Urodynamics: hypocontractile or acontractile detrusor
Under-active
Normo-active
Under-active
Underactive

▲ **Figure 28–3.** Patterns of lower urinary tract dysfunction with neurologic disease. (Reproduced with permission from Panicker JN, Fowler CJ, Kessler TM: Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management. The Lancet. Neurology Jul 2015;14(7):720–732.)

Storage-phase symptoms are the most common LUT symptoms among individuals with MS, with overactive bladder ranging from 26% to 99% (Phe et al, 2016). However, individuals can also demonstrate signs of stress urinary incontinence (56%), mixed urinary incontinence (Murphy et al, 2012), and voiding-phase problems (6–49%) (Betts et al, 1993; Kasabian et al, 1995; Amarenco et al, 1995). Individuals with longer disease duration and greater disease severity often have a higher prevalence of LUT dysfunction; however, correlations between the level of the lesions and the type of LUT dysfunction are difficult to make because of the widespread distribution of lesions that can wax and wane (Mahajan et al, 2010).

▶ Spinal Cord Injury

Spinal cord injury may be complete or incomplete and poses potentially dangerous sequelae to the LUT. After an injury, there is an initial period of spinal shock, lasting anywhere from 6 weeks to 1–2 years in extreme cases. This period of spinal shock is characterized by an absence of somatic reflex activity and flaccid muscle paralysis below the level of the injury, resulting in an acontractile bladder during this time (Wein and Dmochowski, 2016). Once this initial period of shock has resolved, spinal reflexes return, resulting in detrusor overactivity and DSD. This combination of LUT findings can be particularly problematic because of the high pressure that is generated in the urinary tract system, leading to increased risk of upper urinary tract damage (Schops et al, 2015). For spinal cord injuries at or above the level of T6, there is also concern of autonomic dysreflexia, which is a potentially life-threatening condition characterized by an increase in systolic blood pressure, headache, flushing, piloerection, stuffy nose, sweating above the level of the lesion, vasoconstriction below the level of the lesion, and dysrhythmias (Krassioukov et al, 2012).

Neurospinal Dysraphism

Neurospinal dysraphism refers to malformation of the neural tube and collectively refers to spina bifida cystica and spina bifida occulta. Spina bifida cystica includes both myelomeningocele, where the nerve roots or portions of the spinal cord have evaginated beyond the vertebral bodies, and meningocele, which contains only a herniated meningeal sac and no neural components. Myelomeningocele, commonly referred to as **spina bifida**, occurs in approximately 1 per 1000 live births and is the result of neural tube malformation from lack of folate during pregnancy. Among patients with myelomeningocele, 2% have cervical lesions, 5% have thoracic lesions, 26% have lumbar lesions, 47% have lumbosacral lesions, and 20% have sacral lesions (Churchill et al, 2001). It is believed that over 90% of individuals with spina bifida have LUT dysfunction. Even if an individual with spina bifida has normal LUT function, this can change over time as a result of spinal cord tethering. Individuals with spina bifida can have detrusor overactivity, detrusor underactivity, or poor bladder compliance depending on the level of the lesion (Kessler et al, 2006). An areflexic bladder with an open bladder neck is the “typical” finding among the spina bifida population (Wein and Dmochowski, 2016).

McGuire found that myelodysplastic patients with detrusor leak point pressures (DLPPs) greater than 40 cm of water on urodynamics were at higher risk for upper urinary tract deterioration (McGuire et al, 1981). For this reason, close monitoring of this group of patients with urodynamics and upper tract imaging is essential in promoting long-term health and survival.

Cauda Equina Syndrome

The dura opens below the level of L1 into multiple tightly packed thin nerve roots that look like a horse’s tail; hence the name **cauda equina**. The main destination of these nerve roots are the lumbar and sacral plexuses, which provide motor and sensory innervation to the lower limbs and pelvic organs (Berry et al, 1995). Cauda equina syndrome (CES) is characterized by motor and sensory symptoms of the lower limbs, buttocks, and perineum in addition to abnormalities of sexual, bowel, and bladder function (Gitelman et al, 2008). CES is most commonly caused by spinal fractures, disk protrusions, and iatrogenic lesions such as spinal surgery.

Urinary retention associated with an underactive detrusor and loss of bladder sensation are the most common types of LUT dysfunction associated with CES, which occurs immediately following the neurologic insult (DeLong et al, 2008). Overflow incontinence (Kostiuk, 2004) and, less commonly, poor compliance and detrusor overactivity can also occur (Hattori et al, 1992; Podnar et al, 2006).

ASSESSMENT OF NEUROGENIC BLADDER

Assessment of neurogenic bladder is based on the duration, extent, and type of neurologic dysfunction present in each individual. While there are no “one size fits all” guidelines for all types of neurologic LUT dysfunction, all assessments should aim to preserve the upper tracts, minimize lower tract complications, and be compatible with the individual’s lifestyle (CSCM, 2006). Guidelines for the assessment of neurogenic bladder have been developed by the National Institute for Health Care and Excellence (NIHCE) of the United Kingdom (NIHCE, 2012), the European Association of Urology (EAU) (Blok et al, 2015), the International Consultations on Incontinence (ICI) (Drake et al, 2016), and the Consortium of Spinal Cord Medicine with support by the Paralyzed Veterans of America (CSCM, 2006).

History and Physical Examination

A detailed history should factor in urinary tract symptoms, neurologic symptoms and diagnosis (if known), the clinical course of the neurologic disease, bowel symptoms, sexual function, comorbidities, and use of prescription and other medication and therapies. In order to assess the impact of the underlying neurological disease and to help determine what bladder management strategies might be appropriate, assessment of patient mobility, hand function, cognitive function and social support are also important (NIHCE, 2006). Other factors to consider are risk and history of urinary tract infections, decubitus ulcers, and other urologic factors that may contribute to LUT dysfunction such as prostate enlargement in men and urethral hypermobility in women (Drake et al, 2016). Questions regarding sexuality and fertility should also be included (Groen et al, 2016).

A general physical examination should include blood pressure measurement, an abdominal examination, an external genitalia examination in males and a vaginal examination if clinically indicated to look for pelvic floor prolapse in women along with a rectal exam to look for fecal loading or alteration in anal tone. A focused neurological examination is also recommended. This may include assessment of cognitive function, ambulation and mobility, hand function, and lumbar and spinal segment function (NIHCE, 2012), including testing sensation and reflexes in the urogenital area (Groen et al, 2016).

Investigations

A. Urine Testing

Urinalysis and urine culture (where appropriate) are considered helpful in testing for the presence of blood, glucose, protein, leukocytosis, and nitrites. It is imperative not to take samples from leg bags and that samples be clean specimens. Many individuals with neurogenic bladder will have chronic bacterial colonization without symptoms of a UTI, known as

asymptomatic bacteriuria. Consensus statements indicate that bacteriuria should not be treated with antibiotics unless the patient has clinical symptoms or for other medical reasons (Nicolle et al, 20065).

B. Measurement of Renal Function

Measurement of serum creatinine and glomerular filtration rate (GFR) can estimate renal function and may be helpful as part of the assessment in patients with neurogenic bladder; however, since most GFR calculations are indirectly based on muscle mass, renal function is overestimated in those with lower percentages of muscle mass such as those with SCI (Chikkalingaiah et al, 2010).

C. Upper Tract Evaluation

There are few published recommendations for imaging studies of the upper tract in individuals with neurogenic bladder. Among the recommendations that do exist, upper tract evaluation should be performed every 6 months to 1 year in individuals with spinal cord injury (Abrams et al, 2008; Sahai et al, 2011) at baseline and then yearly in individuals with transverse myelitis (Tanaka et al, 2006), at baseline and yearly to every 3 years in individuals with spina bifida (Elliott et al, 2005; Mourtzinos et al, 2010), and appropriate imaging recommendations remain unknown in individuals with multiple sclerosis and Parkinson's disease (Stoffel, 2016). Imaging can include tests that evaluate function, such as renal scans, and those that evaluate anatomy, such as ultrasound, CT scans, and intravenous pyelograms (IVPs) (CSCM, 2006).

D. Urodynamic Investigations

Urodynamic studies can be very helpful in assessing both the bladder and the outlet in individuals with neurogenic bladders. It is important to keep in mind that it is possible for individuals with neurogenic bladder to have upper tract deterioration in the absence of clinical symptoms, and urodynamic testing (particularly with fluoroscopy) can be helpful in making this diagnosis. Testing is particularly important in individuals at high risk for upper tract complications, such as spina bifida and spinal cord injured patients. It is also recommended prior to performing surgical treatments for neurogenic LUT dysfunction (NIHCE, 2012). According to the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guidelines on urodynamics, individuals with neurogenic bladder should receive a post void residual (PVR) assessment, a complex cystometrogram (CMG), pressure flow analysis, fluoroscopy at the time of urodynamics (videourodynamics) when available, and electromyography (EMG) (Winters et al, 2012). During urodynamics, it is important to assess bladder sensation, detrusor function and compliance during filling cystometry, sphincter function during bladder filling, detrusor/sphincter function during voiding, DLPP in patients with impaired compliance, cystometric bladder capacity, and PVR (Drake et al, 2016).

MANAGEMENT OF NEUROGENIC BLADDER

Management of neurogenic bladder should be aimed at preserving upper tract function and improving and/or maintaining a reasonable quality of life in relation to the LUT. Treatments should address both storage and voiding dysfunction, when present. This section discusses some of the most common management strategies for neurogenic bladder: however, this discussion is by no means meant to be exhaustive.

Management of Storage Dysfunction

A. Behavioral and Conservative Treatments

Behavioral treatments are appropriate in cases where correcting faulty habits can be helpful, such as in individuals with cognitive deficits, and potentially in those with motor deficits. Implementation of behavioral treatments, however, often requires support from caregivers to be successful. Timed voiding involves separating toilet visits by fixed intervals of time. Habit retraining involves identifying the natural voiding patterns of a patient with urinary incontinence and prompting the patient to void on a schedule to prevent involuntary leakage. Verbal prompts and positive reinforcement can also be helpful techniques to support these practices (Panicker et al, 2015). Pelvic floor exercises and pelvic floor physical therapy (PFPT) can enhance an inhibitory feedback mechanism to the brain to help suppress the urge to urinate and have been shown to be successful in women with multiple sclerosis (De Ridder et al, 1999).

B. Pharmacotherapy

1. Anticholinergic medications—Anticholinergic medications are the mainstay of pharmacotherapy for individuals with neurogenic detrusor overactivity (level of evidence 1a) (Stohrer et al, 2007) and are considered to be first-line therapy, at times in combination with clean intermittent catheterization (CIC). Anticholinergic medications aim to increase bladder capacity and reduce episodes of urinary incontinence secondary to neurogenic detrusor overactivity (Groen et al, 2016). These medications act by competitively antagonizing the muscarinic acetylcholine receptors in the detrusor, causing detrusor relaxation, lower intravesical pressures, and decreased storage symptoms.

There are two types of muscarinic receptors in the bladder: M_2 and M_3. M_2 receptors are most abundant, but M_3 receptors are functionally more relevant to bladder relaxation. Anticholinergic medications act on these receptors and include oxybutynin (immediate release [IR], extended release [ER], patch, topical gel), tolterodine (IR, ER), trospium chloride (IR, ER), solifenacin, darifenacin, and fesoterodine (Cameron, 2016). Adverse effects of anticholinergic medications most commonly include dry mouth, blurred vision, constipation, tachycardia, and confusion, some or all of which may already be present in the neurogenic patient (Panicker et al, 2015). Difficulty emptying the bladder is another potential adverse event of these medications, which should be considered in any individual who has an elevated PVR and in individuals with multiple sclerosis, stroke, or Parkinson's disease who often maintain their ability to urinate volitionally and are particularly vulnerable in this respect (Cameron, 2016).

Of note, anitmuscarinic medications can be administered intravesically, offering a direct route of application to the bladder, which may enhance the therapeutic effect and compliance in some individuals (Smith, 2016).

According to the NIHCE guidelines, anticholinergic medications should be offered to individuals with spinal cord disease (ie, spinal cord injury or multiple sclerosis) and symptoms of overactive bladder and should be considered in individuals with conditions affecting the brain (ie, cerebral palsy, head injury, or stroke) and symptoms of overactive bladder. It is also recommended to monitor PVRs after starting treatment with an anticholinergic medication and to take into account that these medications can cross the blood-brain barrier, can reduce bladder emptying increasing the risk for urinary tract infection, and can precipitate or exacerbate constipation (NIHCE, 2012).

2. β_3-Adrenoceptor agonists—Over 97% of β-adrenergic receptors in the bladder are of the β_3 type, representing the main method of bladder relaxation in humans (Yamaguchi and Chapple, 2007; Biers et al, 2006). These receptors serve to relax the detrusor muscle, making them an ideal therapeutic target. The selective β_3-adrenoceptor agonist mirabegron was approved in by the Food and Drug Association (FDA) in 2012 for clinical use as an additional medication used to treat overactive bladder symptoms. This medication has limited evidence in the neurogenic bladder population, but like many medications, it has been adopted for use in these patients. The main side effects of this medication are cardiovascular with a mean rise in blood pressure of up to 2.4 mm Hg and small increases in heart rate (Nitti et al, 2013).

3. Desmopressin—Desmopressin is a synthetic analog of arginine vasopressin and acts to reduce urine production and volume-dependent detrusor overactivity by promoting water reabsorption at the distal and collecting tubules in the kidney. It has been shown to help with nocturnal LUT symptoms in patients with both multiple sclerosis (Bosma et al, 2005), with Parkinson's disease (Panicker et al, 2015), and in spinal cord injured patients with higher lesions and high nighttime urine output (Szollar et al, 1995).

Prior to starting a patient on desmopressin, it is important to obtain baseline serum creatinine and sodium levels, which should be monitored throughout the treatment period to ensure that hyponatremia does not develop. This medication should be prescribed with caution in individuals aged ≥65 years and in those with dependent leg edema due to risk of hyponatremia and congestive heart failure (Panicker et al, 2015).

4. Onabotulinumtoxin A—Onabotulinumtoxin A, or Botox, can be a good treatment alternative to anticholinergic medications for detrusor overactivity in neurogenic patients, and was first described by Schurch and colleagues in spinal cord patients in 2000 (Schurch et al, 2000). This treatment can decrease detrusor overactivity and incontinence episodes, in addition to causing an increase in bladder capacity and compliance in some cases.

Onabotulinumtoxin A works by blocking the release of acetylcholine from nerve endings (exocytosis), resulting in the blockage of neural transmission and alteration of afferent sensory input. More specifically, the toxin consists of a heavy chain and a light chain linked by a disulfide bond. The toxin binds to synaptic vesicle protein 2 (SV2) by its heavy chain in the synaptic cleft and is internalized by the nerve terminal. Inside the nerve, it is cleaved into its heavy and light chains, and the light chain enters the cytosol. In the cytosol, the light chain cleaves the attachment proteins involved in the fusion of synaptic vesicles (containing acetylcholine) to the cytoplasmic membrane, thereby inhibiting the release of acetylcholine from the nerve. This attachment protein is called **synaptosome-associated protein 25 kD (SNAP-25)**, and cleavage of SNAP-25 renders the soluble *N*-ethylmaleimide-sensitive factor receptor (SNARE) protein inactive, inhibiting release of achetylcholine (Andersson and Wein, 2016).

Onabotulinumtoxin A can also work via the afferent sensory pathway in neurogenic individuals. In the absence of neurologic disease, afferent output from the bladder is conducted by myelinated Aδ-fibers to the higher brain regions. When these pathways are damaged by neurologic disease, an alternative reflex arc consisting of small unmyelinated C-fibers arises, which can lead to uncontrolled bladder contractions and detrusor overactivity (Fowler et al, 2008). Onabotulinumtoxin A reduces sensory receptor levels in the urothelium, potentially reducing C-fiber stimulation (Sellers and McKay, 2007).

Intradetrusor onabotulinumtoxin A injections are recommended as grade A in the EAU guidelines to treat neurogenic detrusor overactivity once pharmacotherapy has failed (Blok et al, 2015). It is important to consider that these injections may increase the PVR among individuals who void, introducing the need for CIC or other more invasive bladder management strategies. Onabotulinumtoxin A has been extensively studied in the neurogenic population. One systemic review found a significant reduction in maximal intravesical pressure after injection with a mean reduction in detrusor pressure of 40–60% (Karsenty et al, 2008). A placebo-controlled study looking at onabotulinumtoxin A use in individuals with multiple sclerosis and spinal cord injury found that 200–300 units of the toxin significantly reduced the number of urinary incontinence episodes per week (−21.8 for 200 units and −19.4 for 300 units compared to −13.2 for placebo), and improved maximum cystometric capacity, DLPP, and quality of life compared to placebo (Cruz et al, 2011).

C. Neuromodulation

Neuromodulation is a well-established third-line treatment for nonneurogenic overactive bladder, but its use in neurogenic bladder is relatively less established. Neuromodulation is currently performed in two varieties: sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS), both of which received approval form the FDA for use in nonneurogenic overactive bladder in the late 1990s. The neurogenic population was initially excluded from this approval because it was believed that an intact neural system was necessary for its efficacy. Since that time, however, investigators have demonstrated its efficacy among individuals with neurogenic disorders; however, most of the literature consists of studies with small sample sizes and relatively heterogeneous patient populations, making them difficult to interpret (Sanford and Suskind, 2016).

The mechanism behind neuromodulation is not clearly understood. The current leading hypothesis is that neuromodulation works by stimulating peripheral somatic afferent nerves, or C-fibers. SNM stimulates the pudendal afferent nerves, and PTNS stimulates the sensory component of the tibial nerve. It is assumed that this stimulation blocks competing abnormal visceral afferent signals from the bladder and prevents reflex bladder hyperactivity (Wein and Dmochowski, 2016).

Most of the literature on neuromodulation in the neurogenic patient is limited to individuals with stroke, Parkinson's disease, multiple sclerosis, and incomplete spinal cord injury. Success rates in these studies range from 50% to 80%, rivaling those in the nonneurogenic population (Lay and Das, 2012; Kessler et al, 2010; Peters et al, 2013).

▶ Management of Voiding Dysfunction

Voiding dysfunction consists of inability to empty the bladder, which can be due to either failure of the bladder to contract or increased outlet resistance, such as in DSD. While there are several management strategies for voiding dysfunction discussed herein, it is important to note that reflex bladder emptying and bladder emptying using external compression or abdominal straining are not recommended because of the resulting high intradetrusor pressure that can be generated by way of these techniques (Drake et al, 2016).

A. Clean Intermittent Catheterization

Clean intermittent catheterization (CIC) is the recommended first choice for bladder management among individuals who are unable to empty their bladders on their own and who maintain manual dexterity or have a willing caregiver (Drake et al, 2016). CIC is preferable to an indwelling catheter, either a urethral catheter or a suprapubic tube, and has been shown to decrease long-term complications, including hydronephrosis, bladder and renal calculi, and autonomic dysreflexia (Weld and Dmochowski, 2000). CIC does not work well in individuals with abnormal urethral anatomy, a bladder capacity of <200 mL, autonomic dysreflexia, poor cognition, little motivation, or the inability or unwillingness to adhere to a timed catheterization schedule. Potential complications associated with CIC include urinary tract infections, bladder overdistention, urinary incontinence, urethral trauma with hematuria, urethral false passages, urethral strictures, autonomic dysreflexia (in individuals with spinal cord lesions at or above T6), and bladder stones (CSCM, 2006). Current government guidelines recommend employing catheters for a single use only, and there are many catheter styles available, including hydrophilic, coudé, touch-free, and a catheter attached to a collection bag. Many individuals with upper extremity limitations may require adaptive equipment to successfully perform CIC.

B. Indwelling Catheters

The use of indwelling catheters can predispose individuals to complications but does serve as an alternative method of bladder management in some individuals where CIC is not possible or medically advised. If a long-term catheter is required, a suprapubic tube is recommended over a urethral catheter because of decreased urethral complications and patient preference (Drake et al, 2016). The Consortium for Spinal Cord Medicine suggests that indwelling catheterization can be considered for individuals with poor hand skills, high fluid intake, cognitive impairment or active substance abuse, elevated detrusor pressures, lack of success with other less invasive bladder management strategies, need for temporary management of vesicoureteral reflux, and limited assistance from a caregiver, rendering other types of bladder management impossible. Long-term risks of indwelling catheters include bladder and kidney stones, urethral erosion and epididymitis (for urethral catheters), recurrent symptomatic urinary tract infections, incontinence, pyelonephritis, hydronephrosis from bladder wall thickening or fibrosis, and bladder cancer (CSCM, 2006).

C. Sphincterotomy

Sphincterotomy is an option for the treatment of DSD in male spinal cord injured patients with detrusor overactivity refractory to medications and CIC, in addition to those who are unwilling to carry out this bladder management strategy. Sphincterotomy with drainage via a condom catheter is preferable to an indwelling catheter and may be a good option in those who are unable to perform CIC.

Sphincterotomy is a procedure wherein the external urethral sphincter is incised, resulting in significantly lower intravesical pressures, PVRs and a decrease in the occurrence of autonomic dysreflexia. Complications of this procedure can include bleeding, clot retention, urosepsis, erectile dysfunction, and sphincterotomy failure (Hou and Zimmern, 2016). An alternative to surgical sphincterotomy is onabotulinumtoxin A injections into the sphincter at the 3, 6, 9, and 12-o'clock positions around the sphincter (Smith et al, 2005).

D. Reconstructive Surgery

With the introduction of many new treatments over the last several years, reconstructive surgery is becoming less common; however, it remains a viable option when more conservative treatments fail or in certain situations where individuals are unable or unwilling to catheterize. The main indications for reconstructive surgery include hydronephrosis that may be accompanied by progressive renal deterioration secondary to ureteral obstruction from a thick-walled bladder or by ureterovesical reflux, recurrent episodes of urosepsis, and persistent storage or emptying failure when CIC is not possible (Wein and Dmochowski, 2016). Reconstructive surgery includes both continent and incontinent urinary diversions. Continent diversions include the creation of pouches such as the Indiana pouch, the Kock pouch, and the T pouch, and the addition of a catheterizable stoma, such as a Mitrofanoff, to a bladder with or without augmentation. Incontinent diversions consist mainly of ileal and colon conduits (Herschorn and Bailly, 2016).

CONCLUSIONS

Lower urinary tract dysfunction is a common manifestation of many neurologic disorders with predictable symptomatology, based on the location and severity of the neurologic lesion. Our current understanding of the LUT, in states of both health and neurologic disease, continues to grow and evolve, improving both the treatment and prognosis of individuals affected by these disorders.

BIBLIOGRAPHY

Abrams P et al: A proposed guideline for the urological management of patients with spinal cord injury. BJU Int 2008;101(8):989–994.

Aldousari S, Corcos J: Simplified anatomy of the vesicourethral functional unit. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. 3rd ed. CRC Press, New York, 2016, pp. 3–6.

Alonso A, Hernan MA: Temporal trends in the incidence of multiple sclerosis: A systematic review. Neurology 2008;71(2):129–135.

Amarenco G, Kerdraon J, Denys P: [Bladder and sphincter disorders in multiple sclerosis. Clinical, urodynamic and neurophysiological study of 225 cases]. Revue Neurologique 1995;151(12):722–730.

Andersson K-E, Wein AJ: Pharmacologic management of the lower urinary tract storage and emptying failure. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA (eds): Cambell-Walsh Urology. 11th ed., Vol. 3. Elsevier, 2016.

Andersson KE, Arner A: Urinary bladder contraction and relaxation: Physiology and Pathophysiology. Physiol Rev 2004;84(3): 935–986.

Araki I, Kitahara M, Oida T, Kuno S: Voiding dysfunction and Parkinson's disease: Urodynamic abnormalities and urinary symptoms. J Urol 2000;164(5):1640–1643.

Berry M, Bannister LH, Standring SM: Nervous system. In: Williams PL, Bannister LH, Berry MM (eds): Gray's Anatomy. Churchill Livingstone, New York, 1995.

Betts CD, D'Mellow MT, Fowler CJ: Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. J Neurol Neurosurg Psychiatry 1993;56(3):245–250.

Biers SM, Reynard JM, Brading AF: The effects of a new selective beta3-adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder. BJU Int 2006;98(6):1310–1314.

Blok B et al: Guidelines on Neuro-Urology. European Association of Urology, 2015.

Bosma R, Wynia K, Havlikova E, De Keyser J, Middel B: Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder dysfunction: A meta-analysis. Acta Neurol Scand 2005;112(1):1–5.

Cameron AP: Medical management of neurogenic bladder with oral therapy. Transl Androl Urol 2016;5(1):51–62.

Chikkalingaiah KB, Grant ND, Mangold TM, Cooke CR, Wall BM: Performance of simplified modification of diet in renal disease and Cockcroft-Gault equations in patients with chronic spinal cord injury and chronic kidney disease. Am J Med Sci 2010;339(2):108–116.

Churchill BM, Abramson RP, Wahl EF: Dysfunction of the lower urinary and distal gastrointestinal tracts in pediatric patients with known spinal cord problems. Pediatric Clin North Am 2001;48(6):1587-1630.

Consortium for Spinal Cord Medicine (CSCM): Bladder management for adults with spinal cord injury: A clinical practice guideline for health-care providers. J Spinal Cord Med 2006;29(5):527–573.

Cruz F et al: Efficacy and safety of onabotulinumtoxin A in patients with urinary incontinence due to neurogenic detrusor overactivity: A randomised, double-blind, placebo-controlled trial. Eur Urol 2011;60(4):742–750.

de Groat WC, Griffiths D, Yoshimura N: Neural control of the lower urinary tract. Comprehens Physiol 2015;5(1):327–396.

De Ridder D, Vermeulen C, Ketelaer P, Van Poppel H, Baert L: Pelvic floor rehabilitation in multiple sclerosis. Acta Neurol Belg 1999;99(1):61–64.

DeLong WB, Polissar N, Neradilek B: Timing of surgery in cauda equina syndrome with urinary retention: meta-analysis of observational studies. J Neurosurg Spine 2008;8(4): 305–320.

Drake MJ et al: Neurogenic lower urinary tract dysfunction: Clinical management recommendations of the Neurologic Incontinence Committee of the Fifth International Consultation on Incontinence 2013. Neurourol Urodyn 2016;35(6):657–665.

Elliott SP, Villar R, Duncan B: Bacteriuria management and urological evaluation of patients with spina bifida and neurogenic bladder: A multicenter survey. J Urol 2005;173(1):217–220.

Fowler CJ, Griffiths D, de Groat WC: The neural control of micturition. Nat Rev Neurosci 2008;9(6):453–466.

Ghoniem GM, Hairston JC: Neurophysiology of micturition. In: Vasavada SP, Appel RA, Sand PK, Raz S (eds): Female Urology, Urogynecology, and Voiding Dysfunction. Taylor & Francis Group, New York, 2005.

Gitelman A et al: Cauda equina syndrome: A comprehensive review. Am J Orthoped 2008;37(11):556–562.

Groen J et al: Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol 2016;69(2):324–333.

Hattori T, Yasuda K, Sakakibara R, Yamanishi T, Kitahara H, Hirayama K: Micturitional disturbance in tumors of the lumbosacral area. J Spinal Disord 1992;5(2):193–197.

Herschorn S, Bailly GG: Urinary diversion. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. CRC Press, New York, 2016, pp. 545–561.

Hou JC, Zimmern PE: Surgery to improve bladder outlet function. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. 3rd ed. CRC Press, New York, 2016, pp. 531–543.

Karsenty G et al: Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: A systematic literature review. Eur Urol 2008;53(2):275–287.

Kasabian NG, Krause I, Brown WE, Khan Z, Nagler HM: Fate of the upper urinary tract in multiple sclerosis. Neurourol Urodyn 1995;14(1):81–85.

Kessler TM et al: Sacral neuromodulation for neurogenic lower urinary tract dysfunction: Systematic review and meta-analysis. Eur Urol 2010;58(6):865–874.

Kessler TM, Lackner J, Kiss G, Rehder P, Madersbacher H: Predictive value of initial urodynamic pattern on urinary continence in patients with myelomeningocele. Neurourol Urodyn 2006;25(4):361–367.

Kostuik JP: Medicolegal consequences of cauda equina syndrome: An overview. Neurosurg Focus 2004;16(6):e8.

Krassioukov A et al: International standards to document remaining autonomic function after spinal cord injury. J Spinal Cord Med 2012;35(4):201–210.

Lay AH, Das AK: The role of neuromodulation in patients with neurogenic overactive bladder. Curr Urol Rep 2012;13(5):343–347.

Mahajan ST, Patel PB, Marrie RA: Under treatment of overactive bladder symptoms in patients with multiple sclerosis: An ancillary analysis of the NARCOMS Patient Registry. J Urol 2010;183(4):1432–1437.

McGuire EJ, Woodside JR, Borden TA, Weiss RM: Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981;126(2):205–209.

Mourtzinos A, Stoffel JT: Management goals for the spina bifida neurogenic bladder: A review from infancy to adulthood. Urol Clin North Am 2010;37(4):527–535.

Murphy AM, Bethoux F, Stough D, Goldman HB: Prevalence of stress urinary incontinence in women with multiple sclerosis. Int Neurourol J 2012;16(2):86–90.

National Institute for Health and Care Excellence (NIHCE): Urinary Incontinence in Neurological Disease: Management of Lower Urinary Tract Dysfunction in Neurological Disease. London, 2012.

Nicolle LE et al: Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Iinfect Dis 2005;40(5):643–654.

Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE: Urodynamics and safety of the beta(3)-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol 2013;190(4):1320–1327.

Nortvedt MW et al: Prevalence of bladder, bowel and sexual problems among multiple sclerosis patients two to five years after diagnosis. Mult Scler 2007;13(1):106–112.

Panicker JN, Fowler CJ, Kessler TM: Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management. Lancet Neurol 2015;14(7):720–732.

Peters KM, Kandagatla P, Killinger KA, Wolfert C, Boura JA: Clinical outcomes of sacral neuromodulation in patients with neurologic conditions. Urology 2013;81(4):738–743.

Phe V, Chartier-Kastler E, Panicker JN: Management of neurogenic bladder in patients with multiple sclerosis. Nat Rev Urology 2016;13(5):275–288.

Podnar S, Trsinar B, Vodusek DB: Bladder dysfunction in patients with cauda equina lesions. Neurourol Urodyn 2006;25(1):23–31.

Sahai A et al: Neurogenic detrusor overactivity in patients with spinal cord injury: Evaluation and management. Curr Urol Rep 2011;12(6):404–412.

Sanford MT, Suskind AM: Neuromodulation in neurogenic bladder. Transl Androl Urol 2016;5(1):117–126.

Schops TF, Schneider MP, Steffen F, Ineichen BV, Mehnert U, Kessler TM: Neurogenic lower urinary tract dysfunction (NLUTD) in patients with spinal cord injury: long-term urodynamic findings. BJU Int 2015;115(Suppl 6):33–38.

Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D: Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: A new alternative to anticholinergic drugs? Preliminary results. J Urol 2000;164(3 Pt 1):692–697.

Sellers DJ, McKay N: Developments in the pharmacotherapy of the overactive bladder. Curr Opin Urol 2007;17(4):223–230.

Smith CP, Nishiguchi J, O'Leary M, Yoshimura N, Chancellor MB: Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. Urology 2005;65(1):37–41.

Smith CP: Intravesical pharmacologic treatment for neurogenic detrusor overactivity. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. CRC Press, New York, 2016, pp. 489–501.

Stoffel JT: Imaging techniques in the evaluation of neurogenic bladder dysfunction. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. 3rd ed. CRC Press, New York, 2016, pp. 363–371.

Stohrer M, Castro-Diaz D, Chartier-Kastler E, Kramer G, Mattiasson A, Wyndaele JJ: Guidelines on neurogenic lower urinary tract dysfunction. Prog Urol 2007;17(3):703–755.

Szollar S, North J, Chung J: Antidiuretic hormone levels and polyuria in spinal cord injury. A preliminary report. Paraplegia 1995;33(2):94–97.

Tanaka ST, Stone AR, Kurzrock EA: Transverse myelitis in children: Long-term urological outcomes. J Urol 2006;175(5):1865–1868; discussion 1868.

Thavaseelan J, Hamid A: Benign prostatic hyperplasia and lower urinary tract symptoms in men with neurogenic bladder. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. 3rd ed. CRC Press, New York, 2016, pp. 719–729.

Uchiyama T et al: Urinary dysfunction in early and untreated Parkinson's disease. J Neurol Neurosurg Psychiatry 2011;82(12):1382–1386.

Wein AJ, Dmochowski RR: Neuromuscular dysfunction of the lower urinary tract. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA (eds): Campbell-Walsh Urology. 11th ed., Vol. 3. Elsevier, Philadelphia, 2016.

Weld KJ, Dmochowski RR: Effect of bladder management on urological complications in spinal cord injured patients. J Urol 2000;163(3):768–772.

Winters JC et al: Urodynamic studies in adults: AUA/SUFU guideline. J Urol 2012;188(6 Suppl):2464–2472.

Yamaguchi O, Chapple CR: Beta3-adrenoceptors in urinary bladder. Neurourol Urodyn 2007;26(6):752–756.

This page intentionally left blank

Urodynamics

29

Anne M. Suskind, MD, MS, FACS

INTRODUCTION

Urodynamics (UDS) is an interactive study of the lower urinary tract (LUT) that evaluates the transport, storage, and evacuation of urine. UDS is composed of a combination of tests that can be used collectively to obtain functional information about the LUT. The study can be divided up into two main phases: the storage (or filling) phase and the emptying (or voiding) phase. During the storage phase, cystometry is performed and includes measurement of bladder sensation, contractions, compliance, and capacity. Other tests, such as abdominal leak point pressure (ALPP) and detrusor leak point pressure (DLPP), can also be performed when indicated. The emptying phase consists of pressure flow studies and can give valuable information about voiding.

Collectively, the storage and emptying phases of UDS can be enormously helpful in providing objective *sings* to match an individual's *symptoms* when the physical exam findings and other less invasive studies are inconclusive (Abrams et al, 2003). The purpose of UDS, in most cases, is to reproduce and objectively quantify a patient's symptoms to better understand their underlying causes and to aid in diagnosis. In some cases, such as in patients with certain neurologic conditions, individuals may not experience symptoms and urodynamics may be necessary to ensure the safety of urine storage and emptying (Winters et al, 2012).

INDICATIONS FOR URODYNAMICS

Urodynamics should never be performed in isolation, but rather, should be employed when history and physical exam findings do not adequately diagnose or predict the pathophysiology of LUT complaints (Winters et al, 2012), or in cases when an individual has a neurologic condition (eg, spinal cord injury or multiple sclerosis) with a high risk for serious and irreversible upper and lower urinary tract complications.

Prior to each UDS, it is essential that there be a clear indication for the study and a specific clinical question that needs to be answered. Once the question is established, the study should be designed by selecting the appropriate tests to answer this question, and each study should be customized to the individual (Nitti and Combs, 1998). Studies should be performed on the basis of the following "good urodynamic practices":

1. The clinician must have a clear indication for, and appropriate selection of, relevant test measurements and procedures.
2. There must be precise measurement with data quality control and complete documentation.
3. There must be accurate analysis and critical reporting of results (Schafer et al, 2001).

The American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) have published guidelines on urodynamics in adults and offer further guidance for appropriate use of UDS "to assist the clinician in the appropriate selection of urodynamic tests following an appropriate evaluation and symptoms characterization." Their guidelines offer standards, recommendations, and options for the use of these studies in patients with stress-induced urinary incontinence and prolapse, overactive bladder, urgency urinary incontinence, and mixed incontinence, neurogenic bladder, and lower urinary tract symptoms (Table 29–1) (Winters et al, 2012).

COMPONENTS OF URODYNAMICS

Postvoid Residual

Measurement of postvoid residual (PVR) is a simple, noninvasive, and inexpensive way to assess bladder emptying. It can be performed via either ultrasound (bladder scan) or

Table 29-1. Summary of American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guidelines for urodynamics in adults.

Stress-induced urinary incontinence (SUI) and pelvic organ prolapse (POP)
Should assess urethral function (**recommendation**)
Surgeons considering invasive therapy in patients with SUI should assess a postvoid residual (PVR) (**expert opinion**)
May perform urodynamics in patients with both symptoms and physical findings of SUI who are considering invasive, potentially morbid, or irreversible treatments (**option**)
Should perform repeat stress testing with the urethral catheter removed in patients suspected of having SUI who do not demonstrate this finding with the catheter in place during urodynamics (**recommendation**)
Should perform stress testing with reduction of POP in women with high-grade POP but without symptoms of SUI to look for occult SUI and detrusor dysfunction (**option**)
Overactive bladder (OAB), urgency urinary incontinence (UUI), mixed urinary incontinence (MUI)
May perform filling cystometry when it is important to determine whether altered compliance, detrusor overactivity (DO), or other urodynamic abnormalities are present (or not) in patients with UUI in whom invasive, potentially morbid, or irreversible treatments are considered (**option**)
May perform pressure flow studies in patients with UUI after bladder outlet procedures to assess for bladder outlet obstruction (**expert opinion**)
Should counsel patients with UUI and MUI that the absence of detrusor overactivity on a single urodynamic study does not exclude it as a causative agent for their symptoms (**clinical principle**)
Neurogenic bladder
Should perform PVR assessment when appropriate (**standard**)
In patients with relevant neurologic disease at risk for neurogenic bladder, in patients with other neurologic disease and PVR, or in patients with urinary symptoms, clinicians:
    Should perform complex cystometrogram (CMG) (**recommendation**)
    Should perform pressure flow studies during the initial evaluation (**recommendation**)
    May perform fluoroscopy, when available (**recommendation**)
    Should perform electromyography (**recommendation**)
Lower urinary tract symptoms (LUTSs)
May perform PVR as a safety measure to rule out significant urinary retention both initially and during follow-up (**clinical principle**)
Uroflow may be used in the initial and ongoing evaluation of male patients with LUTS when an abnormality of voiding/emptying is suggested (**recommendation**)
May perform filling cystometry when it is important to determine whether DO or other abnormalities of bladder filling/storage are present in patients with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered (**expert opinion**)
Should perform pressure flow studies in men when it is important to determine whether urodynamic obstruction is present in men with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered (**standard**)
May perform pressure flow studies in women when it is important to determine whether obstruction is present (**option**)
May perform videourodynamics in properly selected patients to localize the level of the obstruction, particularly for the diagnosis of primary bladder neck obstruction (**expert opinion**)

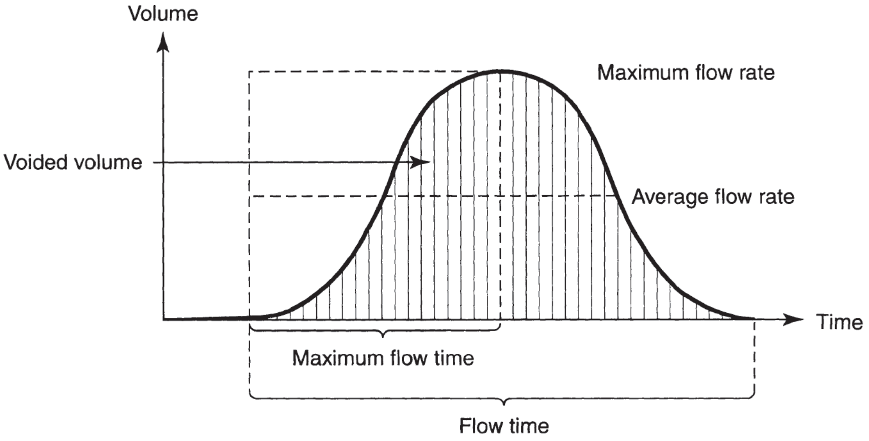
catheterization. PVR should be obtained immediately after a "normal void," as measurements after a "forced void" may be falsely elevated (Brucker and Nitti, 2015). An elevated PVR may be an indication of detrusor underactivity, bladder outlet obstruction, or a combination of the two (Winters et al, 2012); however, this test cannot distinguish between etiologies. There is no one agreed-on value that defines an elevated PVR (values range from 100 to 500 mL in the literature) (Kaplan et al, 2008) and often, elevations in PVRs warrant further testing to examine the possible underpinnings and potential consequences of this finding.

Uroflowmetry

Uroflowmetry is an inexpensive and noninvasive method for "observing" urination. Uroflowmetry assesses urine volume voided per time unit. This study should replicate "normal" voiding as much as possible, being performed in privacy when a patient has a desire to urinate (Schafer et al, 2002), and a PVR should typically be obtained following the uroflow to assess bladder emptying (Rutman and Blaivas, 2007). Patients should be asked whether the uroflow void was representative of their usual voiding pattern (Schafer et al, 2002; Drach et al, 1979).

Uroflowmetry produces the following measurements (Figure 29–1):

- Voided volume (V_V in mL)
- Flow rate (Q in mL/s)
- Maximum flow rate (Q_{max} in mL/s)
- Average flow rate (Q_{av} in mL/s)
- Voiding time (total time during micturition in seconds)
- Flow time (time during which flow occurred in seconds)
- Time to maximum flow (onset of flow to Q_{max} in seconds)



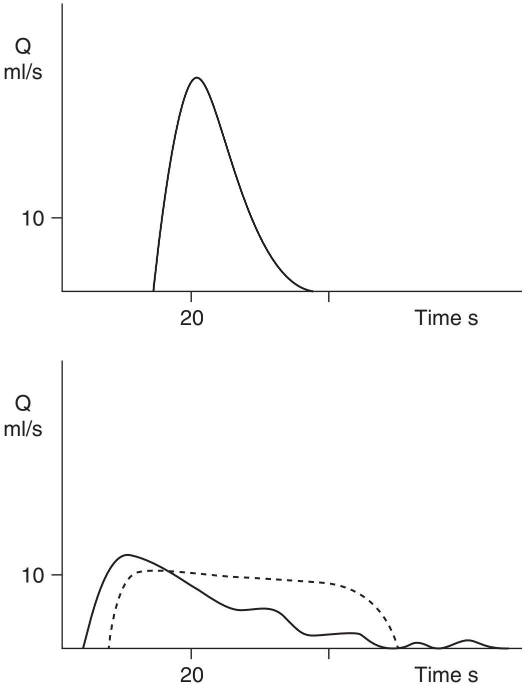
▲ Figure 29–1. Basic elements of uroflowmetry: maximum flow rate (Q_{max}), average flow rate (Q_{av}), flow time, and total voided volume (V_V).

In order to ensure accurate interpretation, there should be a minimum voided volume of 150 mL (Drach et al, 1979). In men, a Q_{max} of >15 mL/s is considered to be normal, less than 10 mL/s is considered to be abnormal, and 10–15 mL/s is considered to be equivocal (Abrams and Griffiths, 1979). In women, a Q_{max} of 20–36 mL/s is considered to be normal (Jorgensen et al, 1998). It is important to consider, however, that uroflow values are known to vary according to age and voided volume in addition to gender (Jorgensen et al, 1998).

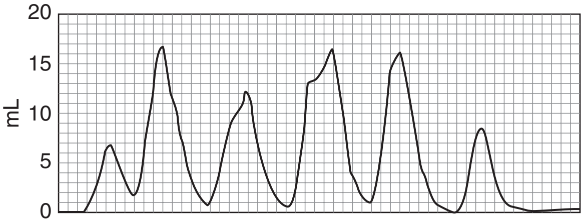
In addition to the numeric values obtained by the uroflow study, it is important to consider the shape of the voiding curve or pattern produced. A normal uroflow pattern is described as a bell-shaped curve that is smooth and without any rapid changes in amplitude (Figure 29–2, top). Examples of obstructive uroflow patterns are illustrated in Figure 29–2 (bottom), which are more "plateau"-shaped (representative of constrictive flow) or "prolonged" in nature (representative of constrictive flow), corresponding to processes such as ureteral strictures and benign prostatic obstruction (BPO), respectively (Schafer et al, 2002). Figure 29–3 represents an abdominal straining or Valsalva uroflow voiding pattern.

Urethral Pressure Profilometry

To maintain continence, it is necessary to ensure that the pressure in the urethra exceeds the pressure in the bladder. If the bladder pressure rises to overcome urethral pressure, leakage of urine may result. Urethral pressure profilometry (UPP) is the measurement of intraluminal pressure along the length of the urethra (Abrams et al, 2003) and provides a measure of the resistance exerted by the urethra. The UPP is designed to differentiate between patients with urinary incontinence based on loss of anatomic urethral support to the urethra from that based on loss of ability to maintain urethral pressure, such as in cases of intrinsic sphincter deficiency (ISD) (Wallach and Ostergard, 2005).



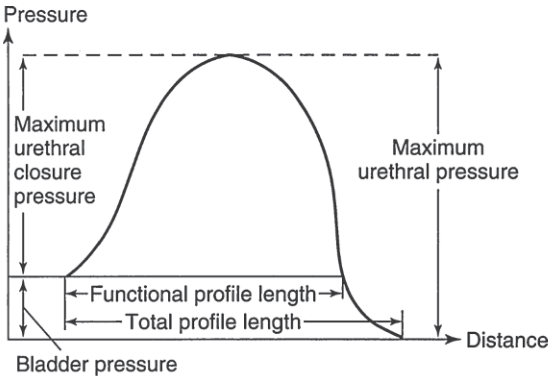
▲ Figure 29–2. A normal uroflow pattern is demonstrated by the bell-shaped curve in the top figure. The bottom figure demonstrates obstructive uroflow voiding patterns; a constrictive voiding pattern is represented by the dotted line, and the solid line represents a compressive voiding pattern. (Reproduced with permission from Schäfer W, Abrams P, Liao L: Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies, Neurourol Urodyn. 2002;21(3):261–274.)



▲ **Figure 29–3.** Uroflow representing abdominal straining/Valsalva voiding pattern.

The UPP is performed using a double- or triple-lumen urethral catheter that allows for the simultaneous recording of both bladder and urethral pressures as a pump of fluid infuses the urethra at a constant rate. Measurement occurs as the catheter is slowly withdrawn along the course of the urethra as the urethral pressure transducer measures the fluid pressure required to just open the closed urethra. The UPP can obtain the following parameters that are illustrated in Figure 29–4 (Brucker and Nitti, 2005):

- **Urethral closure pressure profile:** Measured by the subtraction of intravesical pressure from urethral pressure
- **Maximum urethral pressure:** The maximum pressure of the measured profile
- **Maximum urethral closure pressure (MUCP):** The maximum difference between the urethral pressure and the intravesical pressure
- **Functional profile length:** The length of the urethra along which the urethral pressure exceeds intravesical pressure in women (Abrams et al, 2003)


Pressure
Maximum urethral closure pressure
Maximum urethral pressure
Functional profile length
Total profile length
Distance
Bladder pressure

▲ **Figure 29–4.** Urethral pressure profile and its components. (Reproduced with permission from Bradley WE: Cystometry and sphincter electromyography, Mayo Clin Proc. 1976 Jun;51(6):329–335.)

Electromyography

Electromyography (EMG) evaluates the pelvic floor muscles and the striated urethral sphincter during bladder storage and emptying phases. EMG records the motor unit action potential of the pelvic floor, which is the depolarization of the striated muscle fibers that occurs when the muscle is activated. This activity can be measured via either needle electrodes (less commonly utilized) or surface EMG. During a normal filling/storage phase, EMG activity will either gradually increase (due to the normal guarding reflex) or appear to remain quiet until a voluntary void is initiated, whereby EMG activity should relax. Relaxation of the striated urethral sphincter is the first step of normal voiding, followed by relaxation of the urethra and a rise in detrusor pressure heralding the onset of urine flow (Figure 29–5). Cases where the EMG does not relax during voiding may be indicative of dysfunctional voiding or detrusor external sphincter dyssynergia (DESD) in individuals with a neurologic diagnosis and will be discussed in more detail later in this chapter. Of note, during a stress maneuver, such as cough or a Valsalva maneuver, EMG activity should increase to aid in maintaining continence (Brucker and Nitti, 2015).

Cystometry

The **cystometrogram (CMG)**, or **cystometry**, is a method used to measure the pressure/volume relationship of the bladder during bladder filling. Measurements routinely obtained during cystometry include bladder sensation, contractions, compliance, and capacity (Winters et al, 2012).

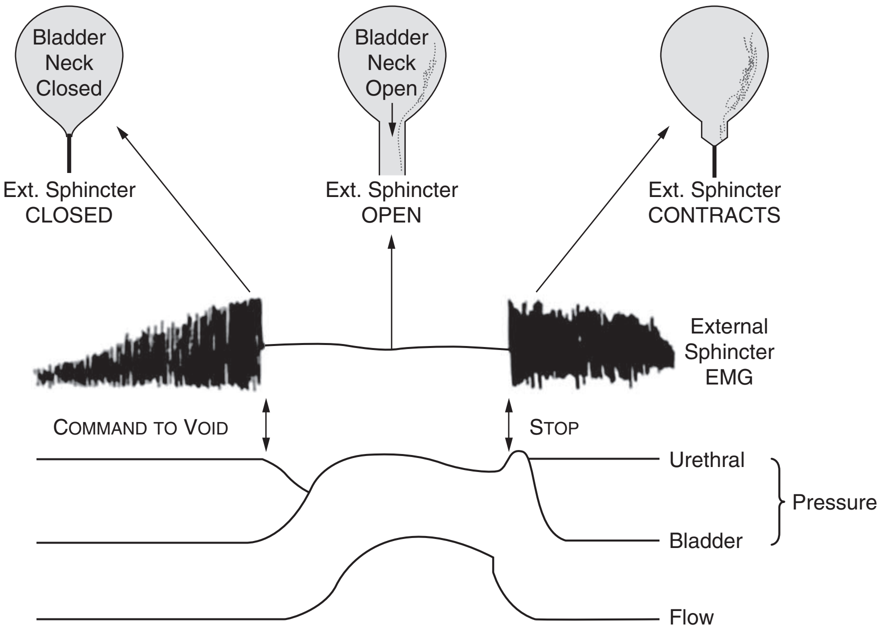
A urethral catheter is required to perform cystometry and is typically 6–8Fr in size and on the basis of various specifications (Schafer et al, 2002). This catheter has a pressure transducer on the end that measures bladder pressure (P_{ves}) by allowing a conversion of an applied pressure into an electrical signal. These catheters can be either water-filled or air-filled (Murphy and Goldman, 2015). Some urethral catheters also have a second transducer that allows for the concurrent measurement of urethral pressures (P_{ura}). The urethral catheter often has a double lumen to allow for simultaneous pressure transduction and bladder filling with water, saline, or radiographic contrast in cases where fluoroscopy is used.

Since the bladder is considered an intra-abdominal organ and experiences pressure effects from the abdomen, a second catheter is often placed per rectum to measure abdominal pressure (P_{abd}). This abdominal catheter typically has a rectal balloon attached to keep it in place. With the presence of this catheter, it is possible to calculate the bladder or detrusor pressure (P_{det}) by the following formula:

$$P_{det} = P_{ves} - P_{abd}$$

A. Performing Cystometry

Before beginning cystometry, the bladder is emptied. Once the bladder is empty and the catheters are in place and zeroed,



▲ **Figure 29–5.** Physiology of micturition. (Reproduced with permission from Blaivas JG. Pathophysiology of lower urinary tract dysfunction, Clin Obstet Gynaecol. 1985 Jun;12(2):295–309.)

filling can begin. Filling rates, type of fluid, and the temperature of the fluid all need to be considered (Schafer et al, 2002; Davis, 1954; Haylen et al, 2010). The position of the patient should also be considered, and it is recommended that studies be performed in the position (sitting versus standing) wherein the individual experiences symptoms.

B. Sensation

Sensation is essential for normal bladder control and may be either reduced (ie, in certain neurologic conditions and diabetic cystopathy) or heightened (ie, in patients with bladder pain syndrome or cystitis) (Jura and Payne, 2015). According to the International Continence Society (ICS), the filling phase of urodynamics starts when filling commences and ends when the patient is given permission to void. Bladder sensation should be assessed during filling with emphasis on first sensation, first desire, and strong desire to urinate. The following are ICS definitions of bladder sensations that should be noted during bladder filling:

- **First sensation:** The feeling that the patient has when s/he first becomes aware of bladder filling
- **First desire:** The feeling that would prompt the patient to urinate at the next convenient time, but urination could be delayed
- **Strong desire:** The persistent desire to urinate without fear of leakage
- **Increased bladder sensation:** An early first sensation of bladder filling and/or strong desire to void that occurs at low bladder volumes and persists
- **Reduced bladder sensation:** Diminished sensation throughout bladder filling.
- **Absent bladder sensation:** No bladder sensation during filling
- **Nonspecific bladder sensations:** Sensations that make the individual aware of bladder filling, such as abdominal fullness
- **Bladder pain:** Abnormal to have pain during filling.
- **Urgency:** The sudden and compelling desire to urinate (Abrams et al, 2003)

Because measurement of sensation is inherently subjective, it is important that there be open and ongoing communication between the patient and the examiner during the study. While there is no standardized method for eliciting information on bladder sensation from patients, practitioners should inquire about bladder sensation in a consistent manner.

There is no agreed-on "normal" volume at which each type of bladder sensation occurs. In one study of 649 neurogenic and nonneurogenic patients, 354 of these individuals experienced three distinct sensations: first sensation at 40% of bladder capacity, first desire to void at 75% of bladder capacity, and a strong desire to void at maximum cystometric capacity (Wyndaele, 1991). Most importantly, observed sensations need to be contextualized for each individual patient.

C. Contractions

Bladder contractions, known by the urodynamic diagnosis of detrusor overactivity (DO), should be assessed during cystometry and should not be present during normal bladder filling. DO is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked (Figure 29–6) (Abrams et al, 2003). DO may be associated with a sense or urgency and/or urgency urinary incontinence and can be further categorized as neurogenic if associated with a neurologic condition (such as spinal cord injury or multiple sclerosis) or idiopathic when there is no clear cause.

The clinical context of DO is very important and the presence or absence of DO on UDS must be interpreted with this context in mind. DO can be artificially test induced in asymptomatic individuals (Heslington and Hilton, 1996), or conversely, it can be absent in up to 50% of symptomatic individuals. For this reason, it is important that the clinician performing the UDS be present and attuned to the patient's sensation during a detrusor contraction on UDS to add context to the clinical significance of these findings (Nitti and Brucker, 2016).

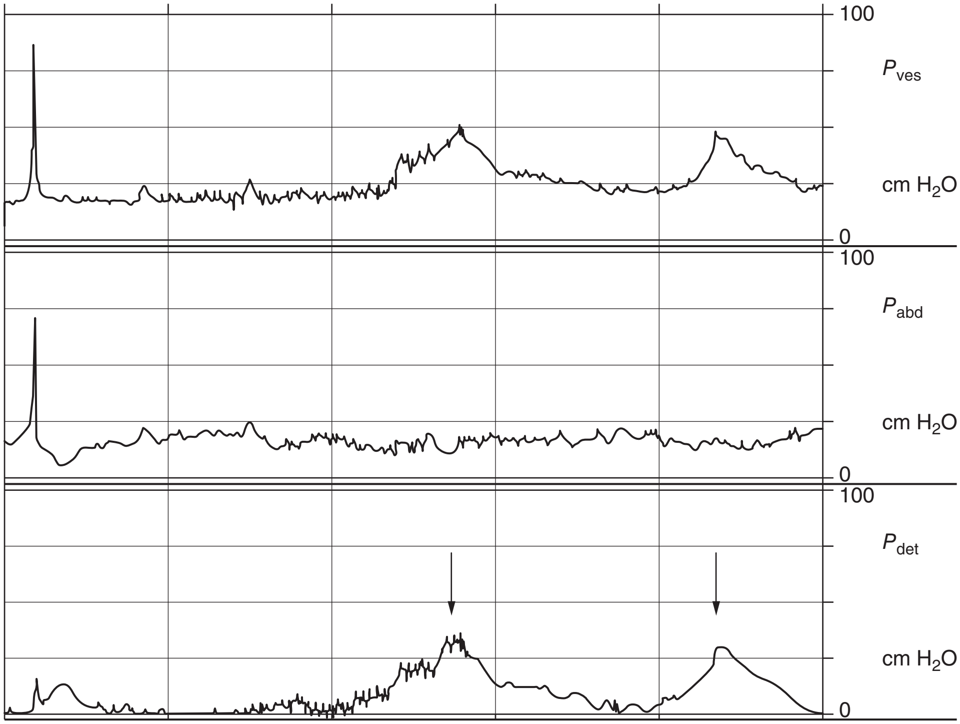
D. Compliance

Compliance in the context here is the relationship between bladder volume and pressure. It is calculated by dividing the change in volume (ΔV) by the change in detrusor pressure (ΔP_{det}) and is expressed in mL/cm H_2O:

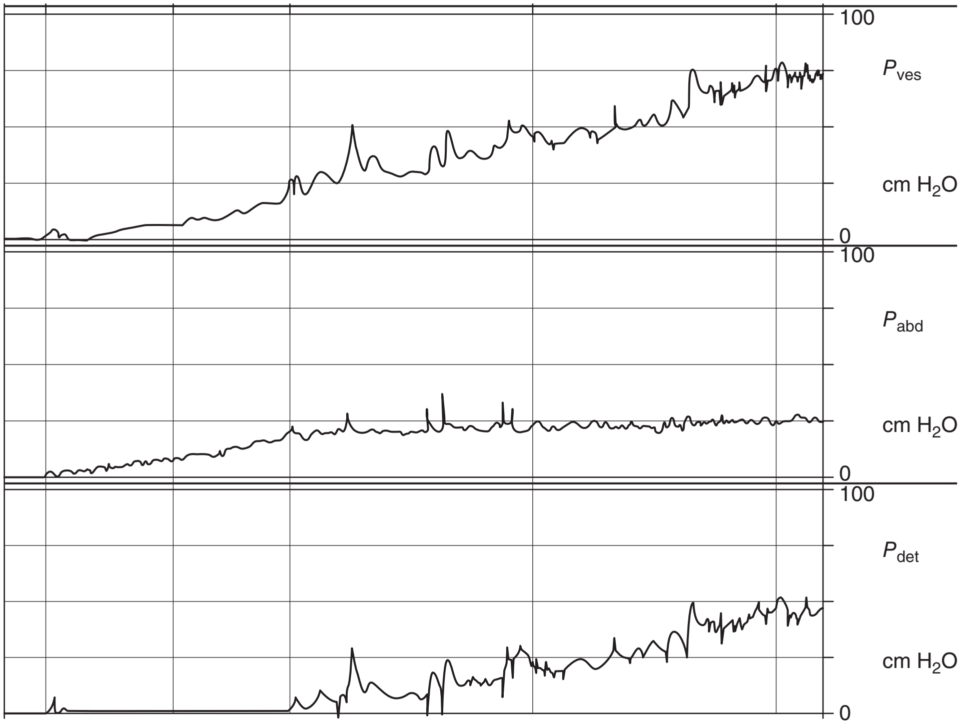
$$C = \Delta V/\Delta P_{det}$$

The ICS recommends measurement of compliance starting at bladder filling (usually zero) and at cystometric capacity or immediately before the start of any detrusor contraction that causes significant leakage (Abrams et al, 2003).

In the normal bladder, compliance is attributed to viscoelastic properties of smooth muscle, collagen, and elastin so



▲ **Figure 29–6.** Filling phase of a UDS study showing involuntary detrusor contractions with (*arrows*). Note that there is a rise in bladder pressure (P_{ves}) and detrusor pressure (P_{det}), but no change in abdominal pressure (P_{abd}). (Reproduced with permission from Corcos J, Ginsberg D, Karsenty G: Textbook of the Neurogenic Bladder, 3rd ed. New York, NY: CRC Press; 2015.)



▲ Figure 29–7. Filling phase of a UDS study showing poor compliance. Note that there is a rise in both vesicle pressure (P_{ves}) and detrusor pressure (P_{det}) as the bladder fills. P_{det} exceeds pressure of 40 cm H_2O. (Reproduced with permission from Corcos J, Ginsberg D, Karsenty G: Textbook of the Neurogenic Bladder, 3rd ed. New York, NY: CRC Press; 2015.)

that as the bladder fills, there is little change in intravesical pressure. Conversely, in poorly compliant bladders, there is a rise in pressure as the bladder fills (Figure 29–7). While there is no one cutoff value ubiquitously used to describe "normal compliance," it has been shown that there is a significant change in the risk of upper tract damage between values of 12.5–15 mL/cm H_2O, suggesting a cutoff value of 12.5 mL/cm H_2O to define abnormal compliance (Weld et al, 2009). Others, however, use a value of 10 mL/cm H_2O to define abnormal compliance (Churchill et al, 1987). While the cutoff value for abnormal compliance is arguable, it is well accepted that a sustained bladder pressure of >40 mL/cm H_2O can cause significant risk to the upper tracts (McGuire et al, 1981). Additionally, it is believed that the amount of time that the bladder is at high pressure is directly proportional to the risk of upper tract deterioration (Churchill et al, 1987).

Compliance is one of the most reproducible and reliable UDS measurements, and arguably, one of the most clinically significant. Poor compliance can lead to upper tract disease and deterioration, including vesicoureteral reflux, upper tract dilation or hydroureteronephrosis, renal impairment, failure and transplant, and even death in extreme cases (McGuire, 2010). Several pathologic conditions that may predispose individuals toward poorly compliant bladders include spina bifida, spinal cord injury (SCI), multiple system atrophy (MSA), damage to the bladder from pelvic surgery and radiation, or bladder outlet obstruction (BOO) (Brown et al, 2015). Early UDS with monitoring of bladder compliance can help to evaluate and even prevent upper tract damage and deterioration in certain individuals and is of great clinical value.

E. Capacity

Cystometric capacity, as defined by the ICS, is the bladder volume at the end of filling cystometry, when "permission to void" is usually given. Maximum cystometric capacity is the volume at which the individual feels that s/he can no longer delay micturition and is associated with a strong desire to void. These definitions differ from maximum anesthetic bladder capacity, which is the volume that the bladder can be filled to under deep general or spinal anesthesia (Abrams et al, 2003).

The purpose of measuring bladder capacity is to estimate the volume of urine that an individual can comfortably hold. Bladder capacity often changes from void to void, and measurement of one bladder capacity during UDS may be imprecise. This information may be augmented by a frequency–volume bladder diary performed over several days (Smith et al, 2015). While there is no one "normal" bladder capacity, it is generally defined as 300–550 mL in adults (Wyndaele, 1999). In children, the following formula can be used to calculate bladder capacity based on age (Feldman and Bauer, 2006):

- For children < 2 years old, bladder capacity in ounces = (2 × years of age) +2
- For children ≥ 2 years old, bladder capacity in ounces = ([years of age]/2)+6

VOIDING PRESSURE FLOW STUDIES

Once the patient's bladder is full and the patient is given permission to void, the emptying phase can begin. This is performed with both the urethral and rectal catheters in place and ideally should be a voluntary void. Of note, some individuals have difficulty voiding during the study in front of the examiner, and this should be contextualized.

During the voiding phase, the pressure–flow study can be used to evaluate both the bladder and the outlet. The bladder is evaluated by assessment of detrusor contractility, and the outlet can be either obstructed or nonobstructed, based on the voiding pattern (previously discussed in the section on uroflowmetry). Pressure–flow studies can identify three fundamental voiding states:

1. Low detrusor pressure and high flow rate (unobstructed)
2. High detrusor pressure and low flow rate (obstructed)
3. Low detrusor pressure with low flow rate (poor contractility) (Nitti, 2005)

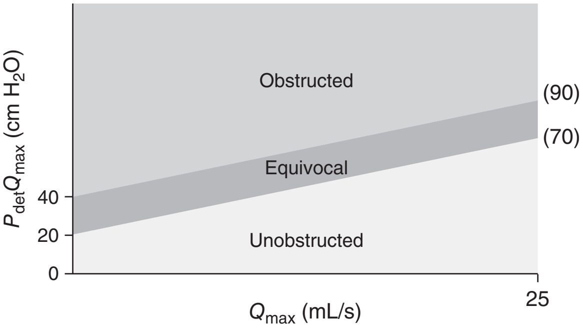
In men, pressure–flow studies are most commonly used to diagnose obstruction due to benign prostatic hypertrophy (BPH), and well-established nomograms to aid in this diagnosis exist. The classic manifestation of BOO is a high-pressure, low-flow void. Abrams and Griffiths described the bladder outlet obstruction index (BOOI) by the following formula:

$$\mathrm{BOOI} = P_{det}Q_{max} - 2(Q_{max})$$

The result is the ICS provisional nomogram, which can be used in the diagnosis of obstruction in men with suspected BPH (Figure 29–8). According to this nomogram, men are obstructed if they have a BOOI of ≥40 and are unobstructed if they have a BOOI of ≤20. BOOIs between 20 and 40 are considered equivocal.

There is also an index of bladder contractility in men that can describe the bladder as strong, normal, or weak. This is called the **bladder contractility index (BCI)** and is calculated by the following formula (Figure 29–9):

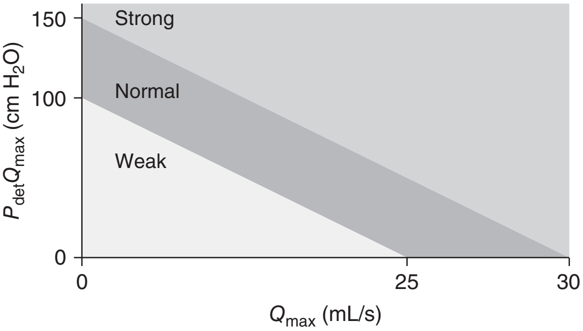
$$\mathrm{BCI} = P_{det}Q_{max} + 5(Q_{max})$$



▲ **Figure 29–8.** The provisional International Continence Society nomogram for the bladder outlet obstruction index (BOOI). (Reproduced with permission from Abrams P: Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function, BJU Int. 1999 Jul;84(1):14–15.)

According to this nomogram, a strong contraction is a BCI that is > 150, normal contractility has a BCI of 100–150, and weak contractility has a BVI of < 100 (Abrams, 1999).

Women can also experience BOO; however, nomograms described in men cannot be applied to women because of differing voiding dynamics and anatomy. Application of these nomograms in women may result in an underestimation of BOO. Women can experience BOO caused by prior incontinence surgery, anterior prolapse, or dysfunctional voiding, among other issues. A Q_{max} of ≤12 mL/s and a $P_{det}Q_{max}$ of ≥25 cm H_2O have been suggested as parameters for BOO in



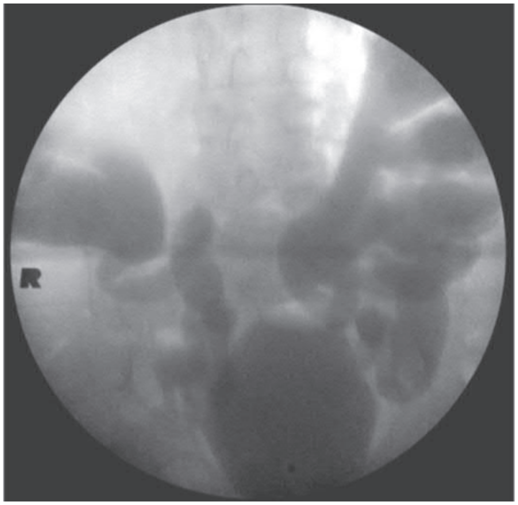
▲ **Figure 29–9.** The bladder contractility nomogram. (Reproduced with permission from Abrams P: Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function, BJU Int. 1999 Jul;84(1):14–15.)

women (Defreitas et al, 2004). The use of fluoroscopy can also be helpful in making this diagnosis in both men and women (Nitti et al, 1999).

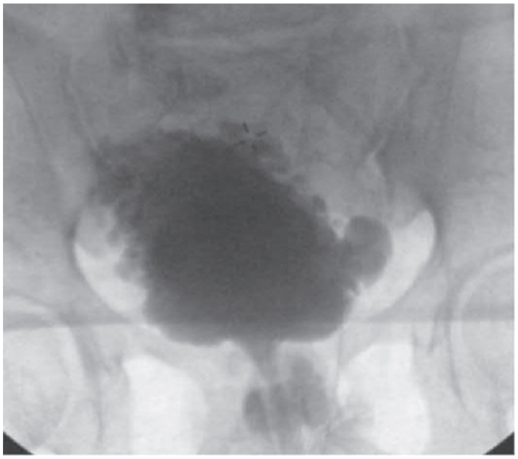
Videourodynamics

The addition of simultaneous imaging to UDS can provide a large amount of anatomic information pertaining to the urinary tract and is referred to as **videourodynamics**. Videourodynamics is typically performed using fluoroscopy (via C-arm) and is particularly helpful in patients with neurogenic bladder, urinary incontinence, and urinary obstruction. Videourodynamics can identify the presence and grade of vesicoureteral reflux in individuals with high-pressure bladders at the volume at which it first occurs. It can also identify potential “popoff” valves such as bladder diverticula (Figure 29–10) and vesicoureteral reflux (Figure 29–11) that may alter the measurement of compliance and should be noted. Videourodynamics can be helpful in identifying leakage of urine during bladder filling and an open bladder neck (Figure 29–12). During voiding, videourodynamics can aid in identifying the level of an obstruction, at either the bladder neck or the urinary sphincter, which may alter management (Brucker and Nitti, 2015).

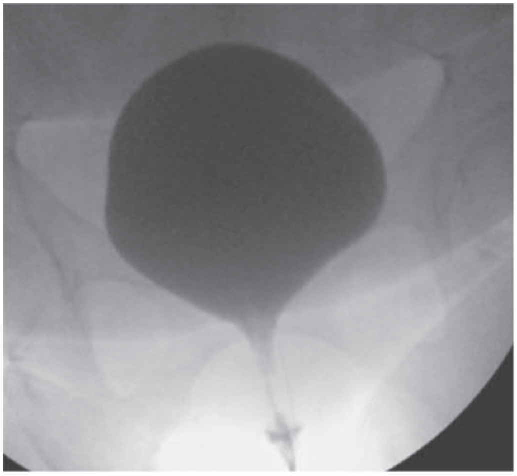
According to the AUA/SUFU guidelines on urodynamics (Table 29–1), the use of simultaneous fluoroscopy is appropriate for assessment of patients with neurogenic bladder to help delineate specific sites of obstruction, identify the presence and grade of reflux and the urodynamic parameters present at the time of reflux, identify anatomic and physical abnormalities (viz, bladder diverticula, bladder outlet abnormalities, and bladder stones), and to help diagnose detrusor external sphincter dyssynergia (DESD), detrusor bladder neck dyssynergia, and other conditions such as primary bladder neck obstruction and dysfunctional voiding, based on grade C evidence (Nager et al, 2012; van Leijsen et al, 2012). The guidelines also support the use of videourodynamics among properly selected patients to localize the level of obstruction for the diagnosis of primary bladder neck obstruction (based on expert opinion) (Winters et al, 2012).



▲ **Figure 29–11.** Fluoroscopic image of vesicoureteral reflux.



▲ **Figure 29–10.** Fluoroscopic image of bladder diverticula.



▲ **Figure 29–12.** Fluoroscopic image of open bladder neck.

OTHER TESTS

Abdominal Leak Point Pressure

Abdominal leak point pressures (ALPPs) are used in the evaluation of stress urinary incontinence (SUI). The urodynamic definition of SUI is "the finding of involuntary leakage during filling cystometry associated with increased intra-abdominal pressure in the absence of a detrusor contraction" (Winters et al, 2012). While studies have shown that UDSs are not necessary for the diagnosis of straightforward SUI in women in whom signs and symptoms of leakage are highly correlated, UDS may be useful in more complex situations. For example, UDS may help distinguish between components of stress and urgency urinary incontinence in individuals with vague clinical complaints potentially leading to different treatment pathways and may also help determine the severity of SUI when potentially different treatment options are available (Suskind and Clemens, 2015).

Abdominal leak point pressure is defined by the ICS as the intravesical pressure at which urine leakage occurs as a result of increased abdominal pressure in the absence of a detrusor contraction (Abrams et al, 2003). McGuire expanded on this definition to explain that ALPP measures "the ability of the urethra to resist abdominal pressures as an expulsive force" (McGuire et al, 1996). Typically, lower ALPPs indicate more severe urinary incontinence; however, in practice, lower ALPPs do not always correlate with symptom severity or treatment outcomes (Lemack, 2004).

There are different methods of measuring ALPPs. Cough leak point pressure (CLPP) is the pressure measured when an individual coughs, and Valsalva leak point pressure (VLPP) is the pressure measured when an individual is asked to perform a Valsalva maneuver. VLPPs often tend to be lower than CLLPs. Different types of pressure (viz, P_{abd}, P_{det}, P_{ves}) can be used to measure ALPPs; however, this measurement was originally described by McGuire to use P_{ves} (McGuire et al, 1996). More important than the type of pressure used is that the pressure is consistently measured the same way in each study, particularly when studies are being reproduced in individuals over time. It is also important to record the lowest pressure that generates leakage as the ALPP (Suskind and Clemens, 2015).

While there is no value or range of values that always correlates to a certain diagnosis, prior research has suggested that an ALPP of <60 mL/H_2O signifies intrinsic sphincter deficiency (ISD), an ALPP between 60 and 90 mL/H_2O is equivocal and an ALPP >90 mL/H_2O signifies little or no ISD (McGuire et al, 1993). It is important to remember that these are just guidelines and that the clinical context must be considered.

Detrusor Leak Point Pressure

The detrusor leak point pressure (DLPP) measurement is a distinctly different from ALPP and is defined by the ICS as the lowest detrusor pressure at which leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure (Abrams et al, 2003). DLLPs are associated with poor compliance and are typically described in the neurogenic population, but can be measured in any individual with poor bladder compliance.

McGuire and colleagues popularized the importance of DLPP in 1981 with the publication of a paper studying urodynamic studies in 42 children with myelodysplasia over a period of 7 years. They reported upper tract damage in a large number of these individuals (68% had vesicoureteral reflux, and 81% had ureteral dilation) related to leakage of urine induced at $P_{det} \geq 40$ cm H_2O, now known as the DLPP (McGuire et al, 1981). While not all individuals will high DLPPs had upper tract deterioration at the time of the report, all (100%) ultimately developed upper tract deterioration when reevaluated 2 years later (McGuire et al, 1983). Once this association between higher DLPP's and poor outcomes was established, clinical outcomes improved with the implementation of various treatments in these individuals (such as intermittent catheterization and anticholinergic use) (McGuire, 2010). Furthermore, measurement of DLPP is extremely important and can improve the long-term health of the urinary tract in certain individuals.

DETRUSOR SPHINCTER DYSSYNERGIA AND DYSFUNCTIONAL VOIDING

Relaxation of the pelvic floor (measured by EMG during urodynamics) is the first step in normal micturition. When involuntary increase in EMG activity at the time of voiding occurs in a patient with a neurologic lesion in the suprasacral spinal cord, DESD results. The ICS defines DESD as a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle, occasionally preventing flow altogether (Abrams et al, 2003).

Detrusor external sphincter dyssynergia often prompts high detrusor pressures to overcome the relatively closed sphincter, representing a high-pressure obstructive voiding pattern that can potentially lead to impaired bladder compliance over time and deterioration of the upper urinary tract (Nitti and Brucker, 2016). DESD occurs when there is a neurologic abnormality between the pontine micturition center (PMC) and the sacral spinal cord (Onufs nucleus), resulting in failed inhibition of the spinal guarding reflexes and erroneous excitation of Onufs nucleus, causing the external urethral sphincter to contract during a detrusor contraction. Neurologic conditions associated with DESD include spinal cord injury, multiple sclerosis, myelomeningocele, and transverse myelitis (Harris et al, 2015).

Poor relaxation of the pelvic floor in an individual without a corresponding neurologic diagnosis is called **dysfunctional voiding**, whereby there is an intermittent and/or fluctuating flow rate due to the involuntary intermittent contractions of the periurethral striated muscle during voiding (Abrams et al, 2003). Symptoms may include long voiding duration, hesitancy, intermittent stream, straining to urinate, recurrent cystitis, enuresis, frequent voiding, pain during voiding, anal discomfort, and even vesicoureteral reflux in some cases (Amarenco et al, 2016).

CLINICAL APPLICATIONS OF URODYNAMICS

Stress-Induced Urinary Incontinence

There have been several studies examining the use of UDS among women with SUI. The Value of Urodynamic Evaluation Trial (ValUE) was a multicenter randomized trial that studied women with straightforward uncomplicated SUI (based on validated questionnaire, PVR < 150 mL, negative urinalysis or culture, or urethral mobility with positive provocative stress test) who were planning to undergo surgery for this problem. Women with a history of prior incontinence surgery, pelvic radiation, pelvic surgery in the last 3 months, or significant anterior or apical pelvic organ prolapse were excluded. A total of 630 women were randomized to preoperative urodynamic studies versus office evaluation alone, and the primary outcome was surgical treatment success measured by questionnaires at 12 months. A total of 76.9% of women who underwent UDS and 77.2% of women who did not undergo UDS reported treatment success at 12 months, consistent with noninferiority, meaning that among women with uncomplicated straightforward SUI, office evaluation alone was not inferior to UDS in terms of treatment success at 12 months status postsurgery (Nager et al, 2012).

Another multicenter study conducted in the Netherlands also examined the value of UDS prior to SUI surgery in women. This study looked at women with predominant SUI who were all eligible for surgical treatment on the basis of clinical assessment alone. All women then underwent UDS. Among women whose UDS findings were discordant with the clinical assessment (eg, SUI was not confirmed, or they had DO, weak flow, elevated PVR, small cystometric maximum capacity, or reduced bladder sensation), participants were randomized to receive either immediate surgery or individually tailored therapy on the basis of the UDS findings (including anticholinergics for DO, pelvic floor exercises or bladder training for dysfunctional voiding, a pessary, expectant management, intradetrusor botulinum toxin injections, or percutaneous tibial nerve stimulation). The women were assessed 12 months later via questionnaire (Urogenital Distress Inventory) with an intention-to-treat analysis. A total of 578 women were included in the study, 46% of whom had discordant UDS findings and were eligible for randomization. Mean improvement at 1 year among the group receiving immediate surgery compared to the group receiving tailored therapy was 44 compared to 39 points on the Urogenital Distress Inventory, so that the difference in mean improvement was 5 points in favor of the group receiving immediate surgery. Furthermore, the study concluded that among women with uncomplicated SUI, immediate midurethral sling surgery was not inferior to individually tailored treatment, based on UDS findings (van Leijsen et al, 2012, 2013).

From the findings of these two studies, it is generally accepted that women with uncomplicated straightforward SUI do not need to undergo preoperative UDS. However, there are many women who do not fit into this category because they have symptoms of mixed urinary incontinence or difficulty with bladder emptying, and who may benefit from UDS. Additionally, some surgeons may alter their surgical approach on the basis of ALPPs obtained during UDS, in which case, these studies may be beneficial to perform. The AUA/SUFU guidelines offer recommendations on UDS for SUI, as summarized in Table 29–1.

Overactive Bladder, Urgency Urinary Incontinence, Mixed Urinary Incontinence

Performing UDS for overactive bladder and urgency urinary incontinence symptoms is most helpful when the diagnosis is in question, when a concomitant problem such as bladder outlet obstruction may coexist, and in certain conditions (eg, neurological conditions, radiation cystitis, or chronic outlet obstruction) where high-pressure storage and poor compliance may exist (Brucker and Nitti, 2015). As discussed earlier in this chapter, up to 50% of individuals with symptoms of overactive bladder may not demonstrate DO on any one UDS study; therefore, interpretation of these findings should be contextualized (Nitti and Brucker, 2016). The AUA/SUFU guidelines for performing UDS in adults with these symptoms are summarized in Table 29–1.

Neurogenic Bladder

Perhaps one of the most important uses of UDS is among individuals with neurologic conditions that may deleteriously affect the bladder and upper urinary tract (eg, spinal cord injury or spina bifida). Among this population, individuals often lack symptoms, or the severity of the symptoms may not necessarily correspond with the prognosis or risk of upper tract deterioration, making UDS an important screening test to ensure the safety of bladder storage and emptying. Alternatively, some individuals may have symptoms of urinary incontinence and or difficulty/inability to empty the bladder. The most important UDS parameters to investigate in this population include bladder compliance, DLPP, and pressure–flow studies evaluating for DESD. The goal of UDS in the neurogenic population can be summarized by the following points (Brucker et al, 2016):

- To document the effect of neurologic disease on the LUT
- To correlate patient symptoms with urodynamic signs
- To assess the presence of urologic risk factors associated with urologic complications (DESD, poor bladder compliance, sustained high-pressure detrusor contractions, vesicoureteral reflux)

Urodynamic findings correlate with the level of the neurologic insult. Individuals with lesions above the level of the brainstem most commonly have DO. Individuals with lesions above the sacrum and below the brainstem often have DO, may have DESD, and can have autonomic dysreflexia if the lesion is above T6. Individuals with sacral lesions often have detrusor areflexia. Neurologic lesions and their corresponding symptoms are discussed in more detail in Chapter 27, on neurogenic bladder.

One reason why UDS studies are so important to perform in the neurogenic population is because early identification of high-pressure storage or DESD can be addressed and progressive urinary tract damage can potentially be avoided. Treatments aim at reducing the pressure of the reservoir and are discussed in more detail in Chapter 27.

The AUA/SUFU guidelines on neurogenic bladder are presented in further detail in Table 29–1. Additionally, the National Institute for Health and Care Excellence (NIHCE) from the United Kingdom offers the following guidelines on UDS in the neurogenic population (NIHCE, 2012):

- Do not offer UDS routinely to people who are known to have a low risk of complications (multiple sclerosis).
- Offer videourodynamics to people who are known to have a high risk of renal complications (spina bifida, spinal injury, anorectal abnormalities).
- Offer urodynamics before performing surgical treatments for neurogenic lower urinary tract dysfunction.

While these guidelines assist in recommending which individuals warrant UDS testing, there is a lack of agreement on the frequency of surveillance and follow up testing among individuals with neurogenic bladder. Frequency of testing is based mainly on clinical context of the type and severity of the neurologic condition, whereby individuals at greatest risk (viz, those with spinal cord injury and spina bifida) require more than routine UDS surveillance.

Lower Urinary Tract Symptoms

Often, UDS can be helpful in unraveling the multiple possible causes of LUTS in men and women such as bladder outlet obstruction, detrusor underactivity, DO, and sensory urgency. Often, starting with noninvasive tests, such as a PVR and uroflow, can be helpful in the evaluation of patients with LUTS, and may prompt further testing with more invasive UDS studies.

Among men with bladder outlet obstruction, it has been shown that UDS can help predict which individuals may have residual storage symptoms such as urinary urgency, urinary frequency, and urgency urinary incontinence after a transurethral resection of the prostate (TURP). These symptoms occur in approximately one-third of cases. One study found a higher risk of postoperative irritative voiding symptoms among men with DO that occurs repeatedly during the study or that occurs at a bladder volume of >160 mL (Kageyama et al, 2000). This information can be helpful in counseling patients prior to TURP surgery and may change treatment decisions among men who are more concerned with their overactive bladders than their voiding symptoms.

The literature regarding the preoperative use of UDS to predict treatment success among men undergoing TURP is mixed and controversial. Several studies support its use (Javle et al, 1996; Rodrigues et al, 2001; Porru et al, 2002), while others report that it is not necessary (Pannek et al, 1998; Kanik et al, 2004). Despite the lack of clear evidence, the AUA/SUFU guidelines state that "clinicians should perform pressure–flow studies in men when it is important to determine whether urodynamic obstruction is present in men with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered" (Winters et al, 2012), based on grade B evidence (Table 29–1).

Women with LUTS and difficulty emptying may also benefit from UDS. Pressure–flow studies in women can help differentiate between obstruction and impaired detrusor contractility. Videourodynamics can also provide additional information pertaining to whether an obstruction is anatomic or functional. Anatomic obstruction, such as a high-grade prolapse or prior sling surgery, can typically be seen using fluoroscopy, whereas functional obstruction, such as dysfunction voiding, can be determined using EMG during pressure flow studies of voiding (Nitti and Brucker, 2016). Further AUA/SUFU recommendations for use of UDS in men and women with LUTS are detailed in Table 29–1.

CONCLUSIONS

Urodynamic studies are a collection of tests that can be used individually or collectively to help answer a clinical question pertaining to the lower urinary tract. There should always be a clear indication (or clinical question) for performing UDS, and when performed selectively and using appropriate methods, UDS can be an invaluable component of the clinical evaluation of men and women with lower urinary tract complaints.

BIBLIOGRAPHY

Abrams P, Cardozo L, Fall M, et al: The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology 2003;61(1):37–49.

Abrams P: Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: Three simple indices to define bladder voiding function. BJU Int 1999;84(1):14–15.

Abrams PH, Griffiths DJ: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Br J Urol 1979;51(2):129–134.

Amarenco G, Ismael SS, Soler JM: Dyssynergic sphincter. In: Corcos J, Ginsberg DA, Karsenty G (eds): Textbook of the Neurogenic Bladder. CRC Press, New York, 2016, pp. 133–137.

Brown ET, Hebert KL, Winteres JC: Baldder filling and storage: "Compliance." In: Rovner ES, Koski ME (eds): Rapid and

Practical Interpretation of Urodynamics. Springer, New York, 2015, pp. 171–184.

Brucker BM, Kelly CE, Nitti VW: Evaluation of neurogenic lower urinary tract dysfunction: Basic urodynamics. In: Corcos J, Ginsberg D, Karsenty G (eds): Textbook of the Neurogenic Bladder. CRC Press, New York, 2016, pp. 373–381.

Brucker BM, Nitti VW: Urodynamic studies: Types and indications. In: Rovner ES, Koski ME (eds): Rapid and Practical Interpretation of Urodynamics. Springer, New York, 2015, pp. 3–25.

Churchill BM, Gilmour RF, Williot P: Urodynamics. Pediatr Clin North Am 1987;34(5):1133–1157.

Davis DM: The hydrodynamics of the upper urinary tract (urodynamics). Ann Surg 1954;140(6):839–849.

Defreitas GA, Zimmern PE, Lemack GE, Shariat SF: Refining diagnosis of anatomic female bladder outlet obstruction: comparison of pressure-flow study parameters in clinically obstructed women with those of normal controls. Urology 2004;64(4):675–679; discussion 679–681.

Drach GW, Layton TN, Binard WJ: Male peak urinary flow rate: Relationships to volume voided and age. J Urol 1979;122(2):210–214.

Feldman AS, Bauer SB: Diagnosis and management of dysfunctional voiding. Curr Opin Pediatr 2006;18:139–147.

Harris CH, Smith PP, Gousse AE: Bladder emptying: Coordination of bladder and sphincters. In: Rovner ES, Koski ME (eds): Rapid and Practical Interpretation of Urodynamics. Springer, New York, 2015, pp. 251–262.

Haylen BT, de Ridder D, Freeman RM, et al: An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29(1):4–20.

Heslington K, Hilton P: Ambulatory monitoring and conventional cystometry in asymptomatic female volunteers. Br J Obstet Gynaecol 1996;103(5):434–441.

Javle P, Jenkins SA, West C, Parsons KF: Quantification of voiding dysfunction in patients awaiting transurethral prostatectomy. J Urol 1996;156(3):1014–1018; discussion 1018–1019.

Jorgensen JB, Colstrup H, Frimodt-Moller C: Uroflow in women: An overview and suggestions for the future. Int Urogynecol J Pelv Floor Dysfunct 1998;9(1):33–36.

Jura YH, Payne CK: Bladder filling and storage: "(Coarse) sensation." In: Rovner ES, Koski ME (eds): Rapid and Practical Interpretation of Urodynamics. Springer, New York, 2015.

Kageyama S, Watanabe T, Kurita Y, Ushiyama T, Suzuki K, Fujita K: Can persisting detrusor hyperreflexia be predicted after transurethral prostatectomy for benign prostatic hypertrophy? Neurourol Urodyn 2000;19(3):233–240.

Kanik EA, Erdem E, Abidinoglu D, Acar D, Akbay E, Ulusoy E: Can the outcome of transurethral resection of the prostate be predicted preoperatively? Urology 2004;64(2):302–305.

Kaplan SA, Wein AJ, Staskin DR, Roehrborn CG, Steers WD: Urinary retention and post-void residual urine in men: Separating truth from tradition. J Urol 2008;180(1):47–54.

Lemack GE: Urodynamic assessment of patients with stress incontinence: How effective are urethral pressure profilometry and abdominal leak point pressures at case selection and predicting outcome? Curr Opin Urol 2004;14(6):307–311.

McGuire EJ, Cespedes RD, O'Connell HE: Leak-point pressures. Urol Clin North Am 1996;23(2):253–262.

McGuire EJ, Fitzpatrick CC, Wan J, et al: Clinical assessment of urethral sphincter function. J Urol 1993;150(5 Pt 1):1452–1454.

McGuire EJ, Woodside JR, Borden TA, Weiss RM: Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981;126(2):205–209.

McGuire EJ, Woodside JR, Borden TA: Upper urinary tract deterioration in patients with myelodysplasia and detrusor hypertonia: A followup study. J Urol 1983;129(4):823–826.

McGuire EJ: Urodynamics of the neurogenic bladder. Urol Clin North Am 2010;37(4):507–516.

Murphy AM, Goldman HB: Urodynamics equipment: selection and training. In: Rovner ES, Koski ME (eds): Rapid and Practical Interpretation of Urodynamics. Springer, New York, 2015, pp. 35–42.

Nager CW, Brubaker L, Litman HJ, et al: A randomized trial of urodynamic testing before stress-incontinence surgery. New Engl J Med 2012;366(21):1987–1997.

National Institute for Health and Care Excellence (NIHCE): Urinary Incontinence in Neurological Disease: Management of Lower Urinary Tract Dysfunction in Neurological Disease. London, 2012.

Nitti VW, Brucker BM: Urodynamic and video-urodynamic evaluation of the lower urinary tract. In: Wein A, Kavoussi LR, Partin AW, Peters CA (eds): Campbell-Walsh Urology. 11th ed, Vol. 3. Elsevier, 2016, pp. 1718–1742.

Nitti VW, Combs AJ: Urodynamics: When, why and how. In: Nitti VW (ed): Practical Urodynamics. Saunders, Philadelphia, 1998, pp. 15–25.

Nitti VW, Tu LM, Gitlin J: Diagnosing bladder outlet obstruction in women. J Urol 1999;161(5):1535–1540.

Nitti VW: Pressure flow urodynamic studies: The gold standard for diagnosing bladder outlet obstruction. Rev Urol 2005;7(Suppl 6):S14–S21.

Pannek J, Berges RR, Haupt G, Senge T: Value of the Danish Prostate Symptom Score compared to the AUA symptom score and pressure/flow studies in the preoperative evaluation of men with symptomatic benign prostatic hyperplasia. Neurourol Urodyn 1998;17(1):9–18.

Porru D, Jallous H, Cavalli V, Sallusto F, Rovereto B: Prognostic value of a combination of IPSS, flow rate and residual urine volume compared to pressure-flow studies in the preoperative evaluation of symptomatic BPH. Eur Urol 2002;41(3):246–249.

Rodrigues P, Lucon AM, Freire GC, Arap S: Urodynamic pressure flow studies can predict the clinical outcome after transurethral prostatic resection. J Urol 2001;165(2):499–502.

Rutman MP, Blaivas JG: Urodynamics: What to do and when is it clinically necessary? Curr Urol Rep 2007;8(4):263–268.

Schafer W, Abrams P, Liao L, et al: Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002;21(3):261–274.

Smith AL, Wang MY, Wein AJ: Bladder filling and storage: "Capacity." In: Rovner ES, Koski ME (eds): Rapid and Practical Interpretation of Urodynamics. Springer, New York, 2015, pp. 155–170.

Suskind AM, Clemens JQ: Bladder filling and storage: "Continence: Stress incontinence." In: Rovner ES, Koski ME (eds): Rapid and Practical Interpretation of Urodynamics. Springer, New York, 2015, pp. 209–225.

van Leijsen SA, Kluivers KB, Mol BW, et al: Can preoperative urodynamic investigation be omitted in women with stress urinary incontinence? A non-inferiority randomized controlled trial. Neurourol Urodyn 2012;31(7):1118–1123.

van Leijsen SA, Kluivers KB, Mol BW, et al: Value of urodynamics before stress urinary incontinence surgery: A randomized controlled trial. Obstet Gynecol 2013;121(5):999–1008.

Wallach SJ, Ostergard DR: Urodynamic assessment: Urethral pressuppre profilometry and PTR. In: Vasavada SP, Appel RA, Sand PK, Raz S (eds): Female Urology, Urogynecology, and Voiding Dysfunction. Taylor & Francis, New York, 2005, pp. 141–155.

Weld KJ, Graney MJ, Dmochowski RR: Differences in bladder compliance with time and associations of bladder management with compliance in spinal cord injured patients. J Urol 2000;163(4):1228–1233.

Winters JC, Dmochowski RR, Goldman HB, et al: Urodynamic studies in adults: AUA/SUFU guideline. J Urol 2012;188 (6 Suppl):2464–2472.

Wyndaele JJ: A clinical study on subjective sensations during bladder filling. Int Urogynecol J 1991;2:215–218.

Wyndaele JJ: Normality in urodynamics studied in healthy adults. J Urol 1999;161(3):899–902.

30

Urinary Incontinence

Tom F. Lue, MD, FACS, ScD (Hon); & Emil A. Tanagho, MD

The worldwide numbers of stress urinary incontinence (SUI) and urgency urinary incontinence (UUI) were projected to affect 167 million (prevalence of 3.3%) and 60 million people (prevalence of 1.21%), respectively by 2018 (Irwin et al, 2011). Urinary incontinence is a major health issue, and the total direct and indirect cost in the United States alone was estimated at $19.5 billion in 2000, of which 75% is designated for the management of women with this condition. Incontinence also results in psychological and medical morbidity, significantly impacting health-related quality of life in a manner similar to other chronic medical conditions including osteoporosis, chronic obstructive pulmonary disease, and stroke. Overall prevalence of female incontinence is reported at 38%, increasing with age from 20–30% during young adult life to almost 50% in the elderly (Anger et al, 2006; Hawkins et al, 2010). The prevalence of stress incontinence peaks in the fifth decade of life, and thereafter the prevalence of mixed and urgency incontinence continues to increase. Several studies conducted in the United States show that stress urinary incontinence is more common in white women than in African-American or Asian-American women (Thom et al, 2006). Advances in the understanding of pathophysiology, as well as development of novel pharmacotherapy and surgical techniques for stress, mixed, and urge incontinence (UI), have redefined contemporary care of this patient group.

The International Continence Society (ICS) and the International Urogynecological Association (IUGA) have proposed standard terminology to be used to describe symptoms, signs, conditions, and urodynamic findings, as well as treatment (Abrams et al, 2003; Haylen et al, 2010). They define the symptom of urinary incontinence as “the complaint of any involuntary loss/leakage of urine.” It is also recommended, when describing incontinence, to specify relevant factors such as type, severity, precipitating factors, social impact, effect on hygiene and quality of life, measures used to contain the leakage, and whether the individual experiencing incontinence desires help.

TYPES OF INCONTINENCE

Incontinence can be transient or chronic. Transient incontinence may occur after vaginal childbirth or during an acute lower urinary tract infection and usually resolves spontaneously. Chronic incontinence can result from a multitude of causes and is often persistent and progressive. From a functional and anatomic perspective, it is intuitive to consider the lower urinary tract as a two-part system: the urinary bladder as a reservoir and the bladder outlet as a sphincteric mechanism. Incontinence occurs when either part or both malfunction. Several common types of incontinence are discussed herein: stress urinary incontinence (SUI), urgency urinary incontinence, mixed urinary incontinence (MUI), neuropathic incontinence, and overflow incontinence (OI).

GENERAL APPROACH

A stepwise management algorithm has been recommended for the management of male and female incontinence by the scientific committee of the 4th International Consultation on Incontinence (Abrams et al, 2010). In principle, the committee recommends an initial management and a specialized management algorithm for all types of incontinence. In initial assessment, one should identify the complicated incontinence group for specialized management. This includes recurrent or total incontinence and incontinence associated with pain, hematuria, recurrent infection, prostate irradiation, and radical pelvic surgery, suspected of fistula and significant postvoid residual. The following groups are suitable for initial management: stress incontinence, urgency incontinence, and incontinence with mixed symptoms. The initial clinical assessment should include general health, lower urinary tract, pelvic floor, symptom scores, quality of life, desire for treatment, physical examination, urinalysis, and postvoid residual urine. The initial management consists of lifestyle intervention, bladder and pelvic floor muscle training, and incontinence products and medications. Specialized management is recommended for patients who failed the abovementioned types of management or those with specialized conditions. The assessment includes urinary tract imaging, urodynamics, and cystourethroscopy, and more invasive treatments including surgery, neuromodulation, and prosthetics may be recommended for these patients.

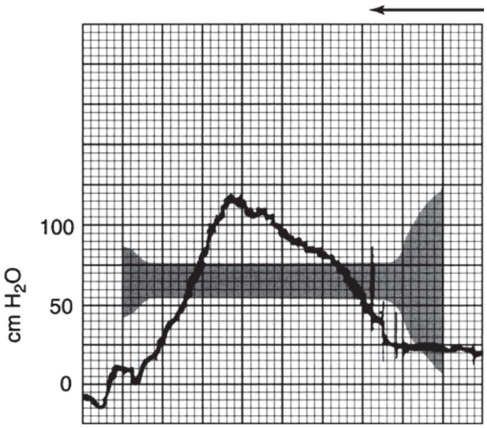
STRESS URINARY INCONTINENCE

The ICS defines **stress urinary incontinence (SUI)** as urine leakage in association with coughing, sneezing, or physical exertion. In men, stress incontinence is mostly due to surgery (eg, after radical prostatectomy) or trauma to the bladder neck or urethral sphincter. The causes of stress incontinence in women are more complicated and somewhat controversial. The vast majority of stress incontinence occurs in women after middle age (with history of vaginal deliveries and obstructed labor). It is usually a result of weakness or disruption of the pelvic floor muscle and ligaments leading to poor support of the vesicourethral sphincteric unit or weakness of the urethral sphincteric tissues. An increase in urethral closure pressure is normally seen during bladder filling; when assuming an upright position; or in stressful events such as coughing, sneezing, or bearing down. During exertion, both passive pressure transmission from increased abdominal pressure and reflex-related contraction of the sphincteric muscles augment urethral resistance to prevent urine leakage.

▶ Anatomy

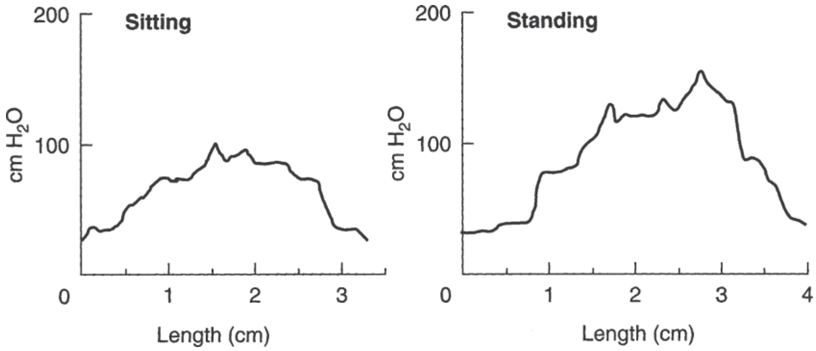
Stress incontinence in women is thought to be caused by two overlapping mechanisms: hypermobility of the bladder neck and urethra and intrinsic sphincter deficiency. In hypermobility, the assumption is that the intrinsic structure of the sphincter itself is intact. It loses closing efficiency because of excessive mobility and loss of support. Thus, the anatomic feature of stress incontinence is hypermobility or a lowering of the position of the vesicourethral segment (or a combination of the two factors). On the other hand, some women who have undergone multiple retropubic or urethral operations have a deficient intrinsic sphincteric mechanism characterized by an open bladder neck and proximal urethra at rest with minimal or no urethral descent during stress. Nevertheless, many women maintain normal continence with hypermobility, and a dynamic magnetic resonance imaging (MRI) study finds no correlation between perineal descent and patients' symptoms of urinary incontinence (Broekhuis et al, 2010). Therefore, contemporary opinion suggests that many women with stress incontinence have varying degrees of intrinsic sphincter deficiency.

Normal continence in women is the product of coordination among the urethra, bladder, pelvic floor muscles, and surrounding connective-tissue elements. Under resting conditions, urethral tone is maintained by smooth and striated muscle activity, tension of the fibroelastic elements in the urethral wall, and the cushioning effect of the soft, compressible submucosal vascular plexus. The urethral pressure profile is a measure of the activity of the external sphincter (Figure 30–1). A static profile demonstrates the resting tonus of both components of the sphincteric mechanism; a dynamic profile gives the responses of these sphincteric elements to various activities, such as an increase in bladder volume, assumption of the upright position (Figures 30–2 and 30–3), the prolonged stress of bearing down, or the sudden stress of coughing and sneezing (Figure 30–4). Normally, the urethral closure pressure—the net difference between the intraurethral and intravesical pressures—is maintained or augmented during stress.



▲ **Figure 30–1.** Normal urethral pressure. Closure pressure at the level of the internal meatus is very low; the pressure rises progressively to reach its maximum at approximately the middle third of the urethra—the site of maximal condensation of striated muscle.

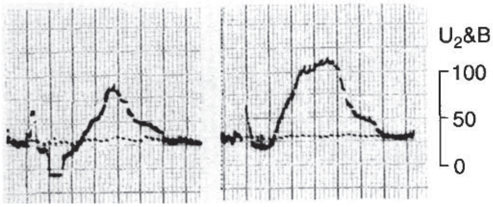
The high rate of success from midurethral sling surgery led some to believe that the midurethral support is the key element in preventing stress incontinence and raised doubts about the relevance of cystographic study. Petros and associates (Petros and Ulmstem, 1990; Petros and Abendstein, 2018) proposed that support of the anterior vaginal wall is provided by three separate but synergistic mechanisms: the anterior pubococcygeus muscle; the bladder neck; and the pelvic floor musculature, which acts like a hammock to help close the bladder neck during stress. Laxity of the anterior vaginal wall causes dissipation of all of three forces, resulting in stress incontinence. Delancey (1994) proposes that the stability of the supporting layer rather than the position of the urethra determines stress continence. During rises in intra-abdominal pressure, the urethra is compressed against the supporting structures, which act like a backboard and



▲ Figure 30–2. Urethral pressure profile for a patient in sitting and upright positions. An approximately 50% increase in urethral closure pressure occurs when the patient assumes the upright position. Urethral functional length is well sustained.

prevent loss of urine. The fact that both bladder neck and midurethral slings have been shown to be successful in treating stress incontinence supports the abovementioned theories (Novara et al, 2010; Ulmsten et al, 1998).

A report of a clinical study concludes that low urethral closure pressure is the best predictor of SUI in women (DeLancey et al, 2008). An MRI study also revealed that the striated urogenital sphincter in women with stress incontinence was 12.5% smaller than that in asymptomatic continent women (Morgan et al, 2009). A study on duloxetine, a serotonin and norepinephrine reuptake inhibitor, showed that it elevates both baseline urethral pressure (adrenergic innervation on the smooth muscle) and active pressure rise with sneezing (Onuf's nucleus)-activated striated muscle contraction (Miyazato et al, 2008). These observations reaffirm the original observation by Tanagho that smooth muscle, striated muscle, and mucosa and submucosal vessels each contribute about one-third of the urethral closure pressure and all are important in sphincter function.

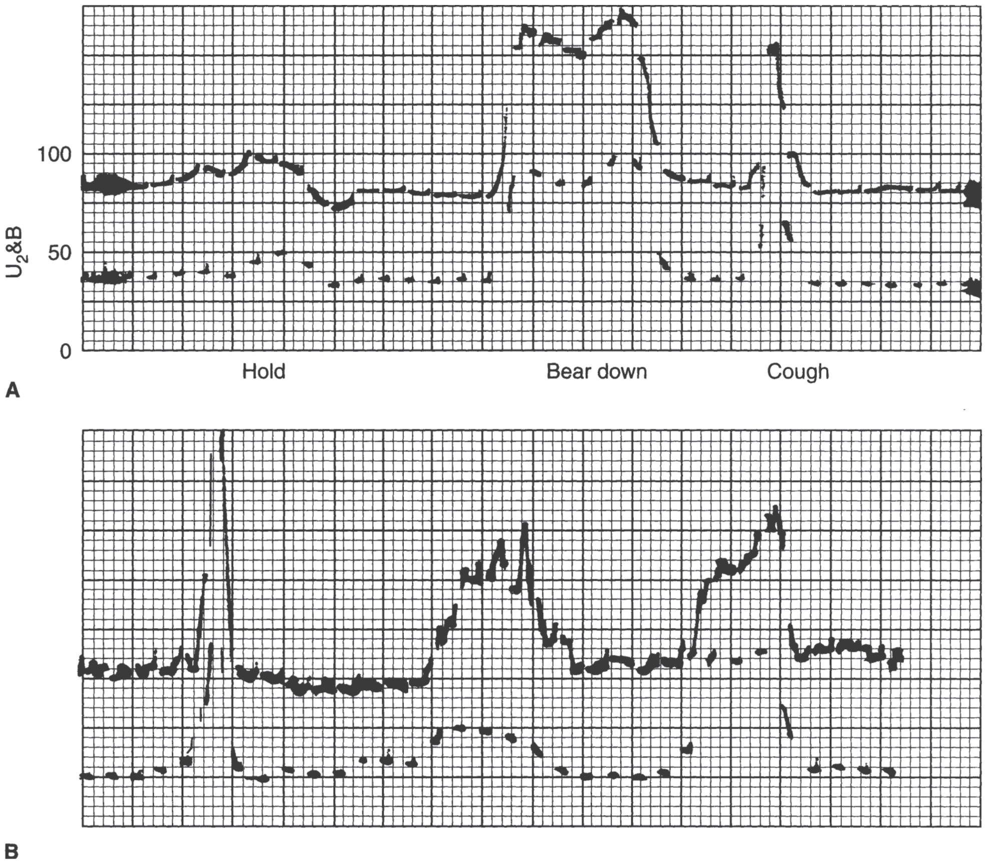


▲ Figure 30–3. Urethral pressure profile in moderately severe stress incontinence; closure pressure with patient in the sitting position with half-distended bladder, then after the upright position is assumed. Note that closure pressure is close to 75 cm H_2O with the patient in the sitting position but decreases to approximately 35 cm H_2O with the upright position. Note also the marked shortening of functional urethral length once the upright position is assumed.

Diagnosis

A detailed history is important, including the degree of leakage; its relation to activity, position, and state of bladder fullness; the timing of its onset; and the course of its progression. SUI occurs at moments of increased abdominal pressure, during coughing, sneezing, and/or straining. If incontinence occurs after a feeling of urgency, without abdominal pressure rise, urge incontinence is likely. Knowledge of past surgical and obstetric history, medications taken, dietary habits, and systemic diseases (eg, diabetes) can be helpful in the diagnosis. A micturition diary that records the time of micturition, voided volume, and type of incontinence is recommended by the ICS as a useful supplement (Abrams et al, 2010). A pad test over 1 hour or 24 hours has also been recommended. In addition, history should also include the degree of bother and effect on quality of life. Many questionnaires and diaries are available for clinical and research use. Validated questionnaires are available to provide more information from patient's perspective on incontinence.

Physical examination is essential, especially if urine leakage is witnessed by the examiner. In women, the pelvic examination demonstrates laxity of pelvic support, presence of any degree of prolapse, cystocele, rectocele, and atrophy or hypermobility of the anterior vaginal wall. A neurologic examination should be done if neuropathy is suspected. Cystographic study for demonstration of the anatomic abnormality is helpful, as is urodynamic study to confirm the classic features of urinary incontinence and determine its cause. The goals of cystographic and urodynamic study are, first, to demonstrate the anatomic abnormality and its extent and, second, to assess the activity of the sphincteric



▲ **Figure 30–4.** ***A:*** Intravesical and urethral pressure responses to the stresses of coughing, bearing down, and the hold maneuver. Note the sharp increase in intra-abdominal pressure reflected in intravesical pressure with coughing and the simultaneous steep increase in urethral pressure. The response is similar with bearing down. Closure pressure is maintained and even augmented during these periods of stress. The hold maneuver (recording membrane is in the proximal urethra) produces a minimal response in closure pressure of the proximal urethra. ***B:*** Recording comparable with that in A, but the membrane is in the midurethra. Note again the sustained closure pressure as a result of coughing and bearing down and the marked pressure increase in the midurethral segment with the hold maneuver.

mechanism and hence the potential for improvement by correcting the anatomic abnormality. The degree of hypermobility in women can also be assessed by a simple Q-tip test (Swift et al, 2010). This is done by inserting a well-lubricated sterile cotton-tipped applicator gently through the urethra into the bladder and then pulling it back to the level of the bladder neck. The angle from the horizontal at rest and after straining is recorded. Hypermobility is defined as a resting or straining angle >30° from the horizontal.

▶ Urodynamic Characteristics of Stress Incontinence

Please refer to Chapter 29, "Urodynamic Studies."

A. Urethral Pressure Profile

The ICS defines urodynamic stress incontinence as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction (Abrams et al, 2003). As would be expected, most patients with stress incontinence have a low urethral pressure profile with reduced closure pressure. This factor varies with the severity of the sphincteric impairment. Not infrequently, this weakness of the pressure profile is not demonstrable when the bladder is relatively empty. It becomes more significant when the bladder has been distended. In addition, the pressure profile may appear normal when the patient is in the supine position; when s/he assumes the upright position, the weakness becomes obvious.

B. Functional Urethral Length

The anatomic length of the urethra is usually maintained, yet the functional length is shorter because of a loss in the proximal urethral segment. Although it might not appear funneled on the cystogram, this segment has very low closure efficiency, and its pressure is almost equal to intravesical pressure. The functional shortening might be minimal or might involve more than one-half of the length of the urethra. It is important to note that the functional length, like the pressure profile, might appear normal when the bladder is not filled or the patient is in the supine position.

C. Response to Bladder Distention and Change in Position

It must be emphasized that, although the features described above might be normal in the resting position with minimal bladder filling, all of them can become aggravated with a full bladder or the upright position.

D. Abdominal Leak Point Pressure

Abdominal leak-point pressure (ALPP) is defined as the intravesical pressure at which urine leakage occurs in the absence of a detrusor contraction (Abrams et al, 2003). This test assesses the intrinsic urethral function, and thus the lower the ALPP, the weaker the sphincter.

▶ Treatment

1. **Conservative management:** In mild and moderate cases, the ICS recommends lifestyle intervention, such as weight loss, caffeine reduction, fluid optimization, pelvic floor muscle training with or without biofeedback, or administration of duloxetine, a serotonin and norepinephrine reuptake inhibitor that has been approved in many countries but not in the United States. Electrical stimulation, intravaginal devices, and urethral inserts may also help some women.
    a. Lifestyle modifications: Obesity has been shown to be associated with SUI. In a randomized trial, women with 8% weight loss had a significant greater decrease in SUI episodes compared to the group with 1.6% weight loss at 6-month follow-up (Subak et al, 2009). Proper fluid management as well as restriction of alcohol and caffeine intake can reduce the leakage amount and episodes of SUI.
    b. Pelvic floor muscle training (PFMT): The classical example is the Kegel exercise. It consists of 8–12 sustained pelvic floor muscle contractions for about 10 seconds each, to be performed several times a day for 4–6 months. Another method teaches women to consciously contract their pelvic floor muscles before and during any increase in abdominal pressure to avert leakage (Aoki et al, 2017). Although one review concluded that 56% were cured after PFMT compared to a cure rate of 6% in the untreated group, evidence of long-term effect and patient adherence after the study is lacking. Nevertheless, the effect of PFMT has been shown to be superior to electrical stimulation and bladder training. Although various biofeedback methods have been proposed to be helpful in some cases, the overall additional benefits are limited (De Vries and Heesakkers, 2018).
2. **Surgery:** If the initial management fails, the principal surgical treatment of female urinary stress incontinence is to provide proper support of the vesicourethral segment or the midurethra.
    a. Bladder neck suspension: There are numerous approaches to restoring the normal position and providing adequate support—some vaginal, others suprapubic. In the suprapubic approach, periurethral tissue is sutured to the back of the pubic symphysis. A modification (Burch procedure) is to fix the anterior vaginal wall to Cooper's ligament. The modification is reported to provide the most lasting results (Drouin et al, 1999; Kulseng-Hanssen and Berild, 2002). The other approach is to suspend the bladder neck with a pubovaginal sling. Many sling materials have been used, including autologous fascia lata or rectus fascia, cadaveric fascia lata, and various synthetic materials. Pubourethral slings are usually placed at the bladder neck to improve urethral coaptation and continence. They are usually performed on patients who failed other types of surgery.
    b. Midurethral tapes: Tension-free vaginal tape (TVT) and many modifications (eg, TVT-O, placed through obturator foramen, or the minislings) are synthetic tapes consisting of propylene with a large pore size to allow tissue ingrowth and fixation; therefore, sutures are not used. The middle of the tape is placed under the midurethra, and the two arms are passed via retropubic space to lie above the rectus fascia or through the obturator foramen to the subcutaneous tissue. Results for TVT with follow-up to 11 years demonstrate comparable or improved versus traditional surgical approaches (urethropexy, Burch colposuspension, or injectable bulking agents) and report success rates of up to 77% (Fong and Nitti, 2010; Novara et al, 2010). In another study Holdø et al (2019) reported overall cumulative cure rates after 1, 5, and 10 years of 92% (95% CI; 90–94%), 79% (95% CI; 75–83%), and 69% (95% CI; 63–75%), respectively. Potential complications include bladder injury, infection, urinary retention, hemorrhage or hematoma, erosion (vaginal or urethral), pain, and dyspareunia. These complications, associated with the use of synthetic tape, have resulted in numerous legal actions against the companies and the surgeons.

c. Intraurethral injection of bulking agents: In patients with significant intrinsic sphincteric damage, local injection of bulking material, such as hyaluronic acid/dextranomer gel, polydimethylsiloxane (Macroplastique), pyrolytic carbon-coated beads suspended in a water-based carrier gel (Durasphere®), and bovine collagen (Contigen), is used to increase the bladder outlet resistance for patients in whom vesicourethral mobility is not excessive and whose primary problem is intrinsic sphincteric weakness (Ghoniem et al, 2010; Lightner et al, 2009). Moreover, autologous myoblasts and fibroblasts, muscle-derived cells, and adult stem cells have been injected into periurethral tissues with mixed results (Mitterberger et al, 2007; Hart et al, 2015; Jankowski et al, 2018). Besides the bulking effect, the injected stem cells seem to be able to stimulate local tissue proliferation (smooth muscle, collagen, and elastic fibers) and thus improve the competence of the sphincter (Lin et al, 2010).

d. Artificial urinary sphincter: This is a saline-filled implantable medical device that consists of three parts: a pressure-regulating balloon, a cuff that is placed around the urethra or bladder neck, and a pump placed in the labia in women and scrotum in men that can open or close the cuff. This device is used mostly in cases that failed other procedures. The overall dry rates at 32 months are around 60% in men after radical prostatectomy (Tutolo et al, 2019). Complications include erosion, infection, urethral atrophy, and device failure.

URGENCY URINARY INCONTINENCE

To better define terms used for various voiding symptoms, the current International Continence Society definitions (Haylen et al, 2010) are as follows:

- **Urgency:** "Urgency is a lower urinary tract (LUT) storage symptom defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer." The term "urge" is used to describe the normal phenomenon of bladder sensations.
- **Urgency (urinary) incontinence (UUI):** Complaint of involuntary loss of urine associated with urgency.
- **Overactive bladder (OAB) syndrome:** Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology. "OAB wet" is associated with UUI, and "OAB dry" is not.

The basic feature of UUI is detrusor overactivity or low bladder compliance and the loss of urine while attempting to inhibit micturition. Sphincteric instability is less common. The focus of this section is restricted to UUI and OAB.

Neurogenic, myogenic, or urothelial bladder dysfunction can lead to UUI or the constellation of symptoms that define OAB. OAB, with or without UUI, is common in both men and women and can result from neuropathic injuries (brain or spinal cord deficit), obstruction, inflammation (interstitial cystitis), diabetes, benign prostatic hyperplasia (BPH), and so on, or be iatrogenic. Bladder overactivity may originate from the urothelium, detrusor muscle, or altered neural activation.

Diagnosis

Assessment of patients with symptoms of UUI, or OAB, should include detailed history, including an assessment of the impact of the disorder on daily life; physical examination; urinalysis; and identification of modifiable causes such as impaired mobility. A sudden urge with uncontrolled loss of urine not associated with physical activity and leak of urine prior to reaching the bathroom are common patient complaints. Most women with uncomplicated urinary incontinence can be given a preliminary diagnosis at this point, and treatment will be initiated. Should initial management fail (usually after an 8–12-week trial), or if complex conditions are present (eg, pelvic organ prolapse, significant postvoid residual, pain, hematuria or pyuria), urodynamics, cystoscopy, or other specialized investigations are recommended (Abrams et al, 2010).

Treatment

The treatment of UUI often progresses from lifestyle change, behavioral techniques (bladder training), to anticholinergic pharmacotherapy. Options for nonresponders to drug therapy may include onabotulinumtoxinA (Botox) bladder injection or implanted sacral nerve stimulation such as InterStim therapy. More invasive surgical procedures, including bladder augmentation or urinary diversion for persistent severe UI, are rarely indicated.

Lifestyle modification includes fluid management, as large volumes can exacerbate urinary incontinence. Behavioral therapy should begin with education about anatomy, physiology, and the patient's individual condition by a bladder dairy. Together with anatomical cartoons, the diary can be used to teach patients about normal bladder function and capacity (and used for goal setting). Four strategies can be employed to regulate bladder function in different patients—bladder training, timed voiding, prompted voiding, and toileting depending on the bladder diary (Potts and Payne, 2018). Optimizing bowel function and eliminating fecal impaction are also important.

Nine oral drugs were given a Grade A Recommendation for Effectiveness based on level 1 evidence by the 6th International Consultation on Incontinence (Abrams et al, 2017): darifenacin, fesoterodine, imidafenacin, propiverine, solifenacin, tolterodine, trospium, oxybutynin, and mirabegron. Among them, all are antimuscarinic agents except mirabegron, which is a β_3-agonist. All antimuscarinic agents have demonstrable efficacy in high-quality clinical trials and have the same general range of antimuscarinic side effects such as dry mouth, stomach upset, and constipation.

There is accumulating evidence that mirabegron has about the same degree of effectiveness as a standard antimuscarinic and that combination therapy with an antimuscarinic can produce improved control of symptoms (Andersson et al, 2018). Because of serious concerns about anticholinergics causing dementia and impaired cognition, mirabegron may be a better choice for treating OAB in the elderly. Concerns about elevated blood pressure and cardiovascular toxicity have largely proven unfounded (White et al, 2018).

Interestingly, phosphodiesterase type 5 inhibitors used for erectile dysfunction have also been reported to be effective in the treatment of lower urinary tract symptoms in men and women (Takahashi et al, 2018; Chen et al, 2017). The proposed mechanism are (1) improvement of LUT oxygenation, (2) smooth-muscle relaxation, (3) negative regulation of proliferation and transdifferentiation of LUT stroma, (4) reduction of bladder afferent nerve activity, and (5) downregulation of prostate inflammation (Gacci et al, 2016).

Although drug therapy is helpful, many patients discontinue therapy because of marginal benefits or undesirable side effects. To meet the needs of these patients, more advanced therapies such as neuromodulation and botulinum toxin therapy have been developed. Neuromodulation therapies activate afferent inhibitory pathways and cortical areas involved in lower urinary tract function. The therapy involves stimulation of the peripheral nerve or sacral nerves. Posterior tibial nerve stimulation (PTNS) is delivered through an acupuncture-type needle for 30 minutes, weekly for 12 weeks. It has been proven superior to sham therapy, and to have reasonably sustained long-term effect (Peters et al, 2013). **Sacral nerve stimulation (SNS)** has been approved by the FDA for treatment of urgency frequency with or without incontinence. It can be effective for even severe and complex cases (Tanagho and Schmidt, 1988). Approximately two-thirds of patients with refractory OAB respond to SNS. International Continence Society has published its best practice statement for use of sacral neuromodulation for various conditions (Goldman et al, 2018).

Botulinum toxin, such as onabotuninumtoxinA (which blocks the release of acetylcholine), is injected into the detrusor muscle via a cystoscope under local anesthesia or light sedation. The effects last for 3–6 months and can be repeated when OAB symptoms recur (Chancellor, 2010). The efficacy appears to be at least similar to SNS (Amundsen et al, 2016).

Although the abovementioned therapies are effective for most patients, in some neurogenic bladder patients with severe spasticity, bladder augmentation, urinary diversion, or chronic catheterization may be needed.

MIXED URINARY INCONTINENCE

Mixed urinary incontinence (MUI) refers to the complaint of an involuntary leakage of urine associated with urgency and with exertion, effort, sneezing, or coughing. This disorder represents an element of detrusor dysfunction (motor or sensory) as well as urethral sphincter insufficiency. Some experts believe that MUI is now the predominant symptom grouping, with rates of upto 50% reported in large population studies (Dmochowski and Staskin, 2005). The relative incidence increases with advancing age and occurs most commonly in women older than 60 years.

Diagnosis

The definition of MUI by the ICS emphasizes the presence of SUI and components of OAB (frequency and urgency) with or without UI, in the absence of known instigating factors. Urodynamically, detrusor overactivity is often noted. However, it should be emphasized that the underlying source of MUI may be a reflex response initiated by urine released into the proximal urethra during stress events. In this way, some individuals with SUI may mimic MUI because of a significant urge component associated with spontaneous urine loss. The diagnostic steps for MUI are the same as for SUI and are described in the section on stress urinary incontinence. In individuals with equal bother (UI and SUI), or difficulty defining their symptoms, urodynamics may help define dysfunction and therapy.

Treatment

The presenting symptoms serve as a guide to initial therapeutic approach. The most bothersome aspect, SUI versus UUI, is usually addressed first. If both types of incontinence are equally bothersome, treatment of the urge component is preferred in most cases.

Initial approaches include behavioral therapy, biofeedback, and treatment with anticholinergics, with approximately 70% of patients experiencing symptomatic improvement; the notable exception is the patient with severe stress incontinence. In men, antimuscarinics for treatment of storage LUTS and prostate enlargement have also been shown to be effective with a less than 3% chance of developing urinary retention (Kaplan et al, 2011). Once the initial treatment response is determined, further therapies can be initiated for persistent or secondary symptoms as outlined in the sections on stress urinary incontinence and urgency incontinence, respectively.

Surgical outcomes for MUI have been reviewed for various sling techniques. Correction of a low-pressure outlet may benefit at least some patients with detrusor overactivity, although results for pure SUI remain superior. MUI symptom resolution has been demonstrated for at least 70% of patients in some series, including a 4-year cure rate of 85% reported for the TVT approach (Dmochowski and Staskin, 2005; Lleberia, 2011). Current data support the use of either midurethral or pubovaginal slings for MUI.

OVERFLOW INCONTINENCE

Overflow incontinence is defined as the involuntary loss of urine associated with bladder overdistension. Two primary processes are involved: (1) urinary retention caused by bladder outlet obstruction and (2) inadequate bladder contractions. Outflow obstruction may be secondary to BPH, bladder neck contracture or urethral stricture, or, less commonly, prostate cancer in men and due to cystocele, pelvic organ prolapse, or previous incontinence surgery in women. Impaired bladder emptying caused by decreased detrusor contractility may be the result of medications, spinal or peripheral nerve injuries, or longstanding overdistension. Diabetic cystopathy can result in overflow incontinence, as both sensory and contractile functions may be compromised. Overflow incontinence may also occur following transurethral prostatectomy (TURP), as urine flow is impeded by urethral stricture or bladder neck contracture.

Diagnosis

A similar approach is followed as outlined previously for the other incontinence subtypes. Reversible causes can usually be identified by patient history. Overflow incontinence is detected by measuring postvoid residual urine volume with ultrasonography (preferred) or urethral catheterization immediately after the patient urinates. Less than 50 mL of urine remains in the bladder immediately following voiding is considered normal. In patient with incontinence and a residual volumes of >200 mL indicates overflow bladder. Urodynamic testing and cystourethroscopy are used to determine the underlying causes.

Treatment

Initial treatment focuses on addressing reversible causes identified during patient evaluation such as cystocele, pelvic organ prolapse, impaired mobility, and urethral stricture.

Should such precipitating elements not be found, outlet obstruction may be treated conservatively, with adjustment of fluid intake and timed voiding. However, male patients will often require further intervention, including pharmacotherapy with α-adrenergic antagonists or 5α-reductase (finasteride)/dual 5α-reductase (dutasteride) inhibitors. If stricture or prostatic obstruction is present, surgical intervention (transurethral resection of prostate, incision of the bladder neck, visual internal urethrotomy) may offer definitive treatment.

For overflow incontinence secondary to nonobstructive underactive detrusor, the first step is to decompress the bladder with an indwelling catheter or clean intermittent catheterization (CIC) for 7–14 days, while addressing potential reversible causes such as medications, infection, or constipation. An α-blocker may be initiated during this time period. Should voiding trials fail repeatedly in the patient with an acontractile detrusor, CIC is the treatment of choice versus a permanent indwelling catheter (if feasible).

NEUROPATHIC INCONTINENCE

Many diseases or conditions involving the brain, spinal cord, and peripheral nerve can affect the function and structure of the bladder and sphincter as well as the synergic action of the two structures. Although complete lesions at different levels of the nervous system may produce typical urodynamic findings, the symptoms of patients suffering from the same lesion may vary as a result of nerve plasticity, secondary changes from infection, fibrosis, or other phenomena. Many diseases can also involve both peripheral and central nervous system to varying degrees. Incontinence can also be due to the patient's inability to respond to a sensory cue from the bladder or having no perception of bladder fullness whatsoever.

A. Failure of Bladder Storage Function

Loss of reservoir function in a contracted bladder can be caused by poor compliance in the detrusor muscle. Intravesical pressure rises with minimal bladder filling, exceeding the outlet resistance and causing urinary leakage. Failure of reservoir function may be found in patients who have a meningomyelocele or exhibit other upper motor neuron lesions. Although these patients may have partial lesions with significant striated sphincteric activity offering some degree of resistance, early loss of bladder compliance increases intravesical pressure with minimal bladder filling and overcomes remaining outlet resistance. These patients, once recognized, must be managed aggressively because they often have a significant risk to the upper urinary tract, such as vesicoureteral reflux, renal deterioration, or lower ureteral obstruction.

B. Failure of Sphincter Function

Complete lesions of the sacral segment or the cauda equina result in a total loss of smooth and striated sphincteric activity. The external sphincter offers minimal resistance. Most patients experiencing such failure can retain some volume, because the bladder musculature becomes atonic and intravesical pressure remains low, but any increase in intravesical pressure can cause leakage, and the bladder never reaches full capacity. Consequently, the integrity of the upper urinary tract is not endangered, as in cases of reservoir failure.

Diagnosis and Treatment

Please see the same sections in Chapter 28: "Neurogenic Bladder."

BIBLIOGRAPHY

Abrams P et al: Standardisation Sub-Committee of the International Continence Society: The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology 2003;61(1):37–49.

Abrams P et al: 4th International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn 2010;29(1):213–240.

Abrams P, et al (eds): Incontinence. 6th ed. ICI-ICS. International Continence Society, Bristol, UK, 2017.

Amundsen CL et al: OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: A randomized clinical trial. JAMA 2016;316(13):1366–1374.

Andersson KE et al: The efficacy of mirabegron in the treatment of urgency and the potential utility of combination therapy. Ther Adv Urol 2018;10(8):243–256.

Anger JT et al: The prevalence of urinary incontinence among community dwelling adult women: Results from the National Health and Nutrition Examination Survey. J Urol 2006;175:601.

Aoki Y et al: Urinary incontinence in women. Nat Rev Dis Primers 2017;3:17042 (doi: 10.1038/nrdp.2017.42); Review. Erratum in: Nat Rev Dis Primers 2017;3:17097.

Broekhuis SR et al: Perineal descent and patients' symptoms of anorectal dysfunction, pelvic organ prolapse, and urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2010;21(6):721–729.

Chancellor MB: Ten years single surgeon experience with botulinum toxin in the urinary tract; clinical observations and research discovery. Int Urol Nephrol 2010;42(2):383–391.

Chen H et al: Efficacy of daily low-dose tadalafil for treating overactive Bladder: Results of a randomized, double-blind, placebo-controlled trial. Urology 2017;100:59–64.

DeLancey JO: Structural support of the urethra as it relates to stress urinary incontinence: The hammock hypothesis. Am J Obstet Gynecol 1994;170(6):1713–1720.

DeLancey JO et al: Stress urinary incontinence: Relative importance of urethral support and urethral closure pressure. J Urol 2008;179(6):2286–2290.

De Vries AM, Heesakkers JPFA: Contemporary diagnostics and treatment options for female stress urinary incontinence. Asian J Urol 2018;5(3):141–148.

Dmochowski R, Staskin D: Mixed incontinence: Definitions, outcomes, and interventions. Curr Opin Urol 2005;15:374.

Drouin J et al: Burch colposuspension: Long-term results and review of published reports. Urology 1999;54:808.

Fong ED, Nitti VW: Review article: Mid-urethral synthetic slings for female stress urinary incontinence. BJU Int 2010;106(5):596–608.

Gacci M et al: Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol 2016;70(1):124–133.

Ghoniem G et al: Durability of urethral bulking agent injection for female stress urinary incontinence: 2-year multicenter study results. J Urol 2010;183(4):1444–1449.

Goldman HB et al: International Continence Society best practice statement for use of sacral neuromodulation. Neurourol Urodyn 2018;37(5):1823–1848.

Hart ML et al: Cell Therapy for stress urinary incontinence. Tissue Eng Part B Rev 2015;21(4):365–376.

Haylen BT et al: International Urogynecological Association; International Continence Society. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29(1):4–20.

Hawkins K et al: The prevalence of urinary incontinence and its burden on the quality of life among older adults with Medicare supplement insurance. Qual Life Res 2010;20(5):723–732.

Holdø B et al: The retropubic tension-free vaginal tape procedure: Efficacy, risk factors for recurrence and long-term safety. Acta Obstet Gynecol Scand 2019.

Irwin DE et al: Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011;108(7):1138–1139.

Jankowski RJ et al: A double-blind, randomized, placebo-controlled clinical trial evaluating the safety and efficacy of autologous muscle derived cells in female subjects with stress urinary incontinence. Int Urol Nephrol 2018;50(12):2153–2165.

Kaplan SA et al: Antimuscarinics for treatment of storage lower urinary tract symptoms in men: A systematic review. Int J Clin Pract 2011;65(4):487–507.

Kulseng-Hanssen S, Berild GH: Subjective and objective incontinence 5 to 10 years after Burch colposuspension. Neurourol Urodyn 2002;21:100.

Lightner D et al: Randomized controlled multisite trial of injected bulking agents for women with intrinsic sphincter deficiency: Mid-urethral injection of Zuidex via the Implacer versus proximal urethral injection of Contigen cystoscopically. Urology 2009;74(4):771–775.

Lin G et al: Treatment of stress urinary incontinence with adipose tissue-derived stem cells. Cytotherapy 2010;12(1):88–95.

Lleberia J et al: Surgical treatment of mixed urinary incontinence: Effect of anterior colpoplasty. Int Urogynecol J Pelvic Floor Dysfunct 2011;22(8):1025–1030.

Mitterberger M et al: Autologous myoblasts and fibroblasts for female stress incontinence: A 1-year follow-up in 123 patients. BJU Int 2007;100(5):1081–1085.

Miyazato M et al: Effect of duloxetine, a norepinephrine and serotonin reuptake inhibitor, on sneeze-induced urethral continence reflex in rats. Am J Physiol Renal Physiol 2008;295(1):F264–F271.

Morgan DM et al: Urethral sphincter morphology and function with and without stress incontinence. J Urol 2009;182(1):203–209.

Novara G et al: Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol 2010;58(2):218–238.

Peters KM et al: Percutaneous tibial nerve stimulation for the long-term treatment of overactive bladder: 3-year results of the STEP study. J Urol 2013;189(6):2194–2201.

Petros PE, Ulmsten UI: An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl 1990;153:7–31.

Petros P, Abendstein B. Knowledge of urethral closure mechanics helps to optimize surgical methodology of the midurethral sling operation. Cent Eur J Urol 2018;71(3):334–337.

Potts JM, Payne CK: Urinary urgency in the elderly. Gerontology 2018;64(6):541–550.

Subak LL et al: PRIDE Investigators. Weight loss to treat urinary incontinence in overweight and obese women. New Engl J Med 2009;360(5):481–490.

Swift S et al: Test-retest reliability of the cotton swab (Q-tip) test in the evaluation of the incontinent female. Int Urogynecol J Pelvic Floor Dysfunct 2010;21(8):963–967.

Takahashi R et al: Tadalafil improves symptoms, erectile function and quality of life in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (KYU-PRO Study). Low Urin Tract Sympt 2018;10(1):76–83.

Tanagho EA, Schmidt RA: Electrical stimulation in the clinical management of the neurogenic bladder. J Urol 1988;140(6):1331–1339.

Thom DH et al: Differences in prevalence of urinary incontinence by race/ethnicity. J Urol 2006;175(1):259–264.

Tutolo M et al: Efficacy and safety of artificial urinary sphincter (AUS): Results of a large multi-institutional cohort of patients with mid-term follow-up. Neurourol Urodyn 2019;38(2):710–718.

Ulmsten U et al: A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 1998;9(4):210–213.

White WB et al: Cardiovascular safety of the β(3)-adrenoceptor agonist mirabegron and the antimuscarinic agent solifenacin in the SYNERGY Trial. J Clin Pharmacol 2018.

Disorders of the Adrenal Glands

31

Michelle L. McDonald, MD; &
Christopher J. Kane, MD, FACS

The adrenal cortex is composed of three zones with distinct endocrine functions: zona glomerulosa (produces mineralocorticoids), zona fasciculata (produces glucocorticoids), and zona reticularis (produces sex steroids). The adrenal medulla accounts for approximately 10% of the gland and is composed of chromaffin cells that secrete catecholamines. Disturbances to the hypothalamic–pituitary–adrenal axis (Figure 31–1) result in classic endocrine disorders such as Cushing's syndrome, hyperaldosteronism, and catechol excess from pheochromocytoma (see Tables 31–1 and 31–2). The diagnosis of these disorders requires careful endocrine and radiographic evaluation.

INCIDENTALOMA

Adrenal "incidentalomas" represent the unsuspected adrenal mass detected on cross-sectional imaging performed for an unrelated reason, and provide the most common presentation of all adrenal masses. The NIH and American Association of Endocrinologists recommend that each incidentaloma be evaluated for metabolic function and malignant potential unless it is an obvious myelolipoma. The differential diagnosis is quite broad (Table 31–3) and includes benign adenoma, functional adrenal tumors, metastasis and benign adrenal lesions such as myelolipoma, and neurofibroma. A systematic approach is required to differentiate functional adrenal masses that warrant removal and those lesions with a significant risk of carcinoma from the more common benign nonfunctional adenoma.

Metabolic Evaluation

A careful history and physical examination with focus on obesity pattern, virilization, glucose intolerance, and hypertension is warranted. Hormone assessment should begin with a test for cortisol hypersecretion (Cushing's syndrome) with three first-line tests available for use: overnight low-dose dexamethasone suppression test, late-night salivary cortisol test, and traditional 24-hour urine-free cortisol test. Patients should also have free-fractionated plasma metenephrines or the 24-hour urinary fractionated metanephrine test to rule out pheochromocytoma. If hypertension and an abnormal plasma aldosterone to renin ratio exist, further tests for primary aldosteronism are indicated. Laboratory examination with serum electrolytes including glucose and potassium should also be done. Additional metabolic tests are performed when there are suspicious signs or symptoms or when screening tests are abnormal.

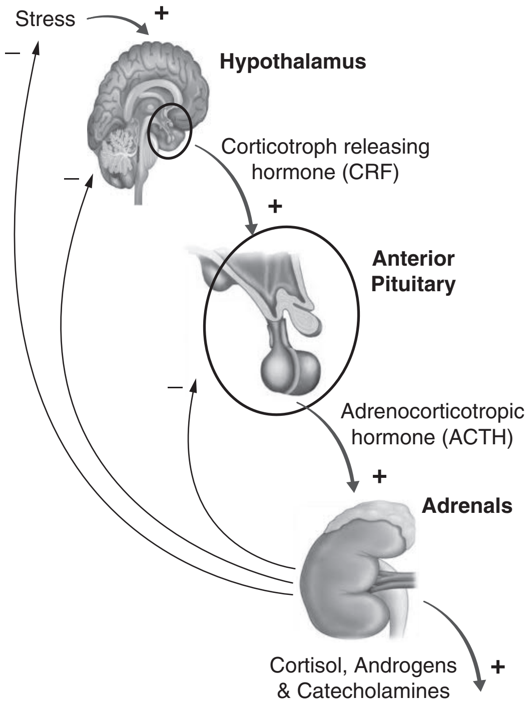
Imaging

Lesions that are primarily cystic on CT or MRI are typically benign and can be followed with serial imaging. Benign adrenal cysts are characterized by thin nonenhancing walls; fluid attenuation on CT and thin calcifications may be present peripherally in about 50% of cases.

Benign adrenal adenomas often have abundant intracytoplasmic lipid and demonstrate low attenuation on noncontrast CT (Hounsfield units [HU] < 10) (see Figure 31–10, later in the chapter). On contrast enhanced CT using washout kinetics, adenomas typically tend to washout > 50% after 10–15 minutes, whereas malignant tumors do not. Lipid-poor adenomas may have greater baseline attenuation on nonenhanced CT but will have similar early contrast washout. Chemical shift imaging is an MR technique to identify intracellular lipid and may be used to identify adenomas; however, CT washout studies demonstrate greater sensitivity and specificity and are considered the gold standard.

Masses with gross fat on CT (ranging from −10 to −20 HU) are myelolipomas (see Figure 31–9, later in the chapter), benign nonfunctional adrenal lesions with lipid and myeloid components. Myelolipomas are usually asymptomatic or present with pain if they bleed.

Characteristics suspicious for malignancy include solid masses that are larger than 4 cm, heterogeneous, hemorrhagic, or necrotic. Such lesions typically enhance on noncontrast


Stress
+
–
Hypothalamus
Corticotroph releasing hormone (CRF)
–
+
Anterior Pituitary
–
Adrenocorticotropic hormone (ACTH)
+
Adrenals
Cortisol, Androgens & Catecholamines
+

▲ **Figure 31–1.** The hypothalamic pituitary adrenal axis.

CT (HU > 25) and have delayed washout (>50%) on contrast enhanced CT. MRI is usually heterogeneous on T1- and T2-weighted images as a result of internal bleeding. Adrenal metastases may have similar appearance to primary malignant adrenal tumors.

▶ Diagnostic Algorithm

Percutaneous CT-guided biopsy may be appropriate for adrenal masses with imaging characteristics suspicious for metastasis or in patients with known malignancy. Pheochromocytoma and adrenocortical carcinoma should be excluded prior to biopsy, to avoid the potential for hypertensive crisis and tumor seeding, respectfully. All functional adrenal masses and those measuring >4 cm should be removed. Laparoscopic adrenalectomy is the preferred technique and is used in most cases except for very large masses suspicious for malignancy or with evidence of local extension. Nonfunctional adrenal masses <4 cm require radiographic reevaluation at 3–6 months and then annually for 1–2 years, as well as hormonal reevaluation annually for 5 years. Surgical resection should be considered if the lesion develops functionality or if it increases in size by ≥0.8 cm. In patients with "subclinical" Cushing's syndrome, surgery should be considered in younger patients or those with worsening metabolic parameters.

Table 31–1. 24-Hour urine measurements in patients with pheochromocytoma.

Urine
  Norepinephrine: 10–100 μg/24 h
  Epinephrine: Up to 20 μg/24 h
  Normetanephrine and metanephrine: <1.5 mg/24 h
  Vanillylmandelic acid (VMA): 2–9 mg/24 h
Plasma
  Norepinephrine: 100–200 pg/mL
  Epinephrine: 30–50 pg/mL

Data from Stein PP, Black HR: A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience, *Medicine* (Baltimore) 1991 Jan;70(1):46–66.

Table 31–2. Catecholamines in urine and plasma.

	Normal no. (%)	1–2X elevated no. (%)	>2X elevated no. (%)
VMA (*n* = 384)	41 (11)	86 (22)	257 (67)
MN (*n* = 271)	12 (5)	33 (12)	226 (83)
UFC (*n* = 319)	14 (4)	30 (10)	275 (86)

VMA, vanillylmandelic acid; MN, metanephrine; UFC, urinary-free cortisol.

Note: The values listed represent the means of the normal ranges, which vary for each laboratory.

Reproduced with permission from Stein PP, Black HR: A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience, *Medicine* (Baltimore) 1991 Jan; 70(1):46–66.

DISEASES OF THE ADRENAL CORTEX

CUSHING'S SYNDROME

Cushing's syndrome is the clinical disorder caused by chronic exposure to excess glucocorticoids, which can be from either exogenous corticosteroids or an endogenous

Table 31–3. Differential diagnosis of adrenal incidentaloma.

Adenoma
Metastasis
Lymphoma
Pheochromocytoma
Neuroblastoma
Adrenocortical carcinoma
Hematoma
Myelolipoma
Adrenal hyperplasia
Adrenal cyst
Granulomatous disease
Hemangioma
Ganglioneuroma

source of cortisol. Endogenous sources can be divided between adrenocorticotropic hormone (ACTH)-dependent (from a pituitary or other ectopic tumor [80%]), and ACTH-independent overproduction of cortisol (adrenal source [20%]). Most cases of the ACTH-dependent form are due to pituitary ACTH secretion (Cushing's disease), and only about 10% of cases are due to the ectopic production of ACTH from nonpituitary tumors. Ectopic ACTH production occurs most frequently in small-cell lung carcinoma; other tumors producing ACTH include carcinoids (lung, thymic, gastrointestinal tract), islet cell tumors of the pancreas, medullary thyroid carcinoma, pheochromocytoma, and small-cell carcinoma of the prostate. Adrenal adenoma and carcinoma can produce excess cortisol resulting in ACTH suppression. In young children, adrenocortical carcinoma is the most common cause of Cushing's syndrome.

Pathophysiology

Overproduction of cortisol by adrenocortical tissue leads to a catabolic state. This causes liberation from muscle tissue of amino acids, which are transformed into glucose and glycogen in the liver by gluconeogenesis. The resulting weakened protein structures (muscle and elastic tissue) cause a protuberant abdomen and poor wound healing, generalized muscle weakness, and marked osteoporosis, which is made worse by excessive loss of calcium in the urine.

In addition, glucose is transformed largely into fat and appears in characteristic sites such as the abdomen, supraclavicular fat pads, and cheeks. There is a proclivity for diabetes, with an elevated fasting plasma glucose level in 20% of cases and abnormal glucose tolerance in 80% of patients.

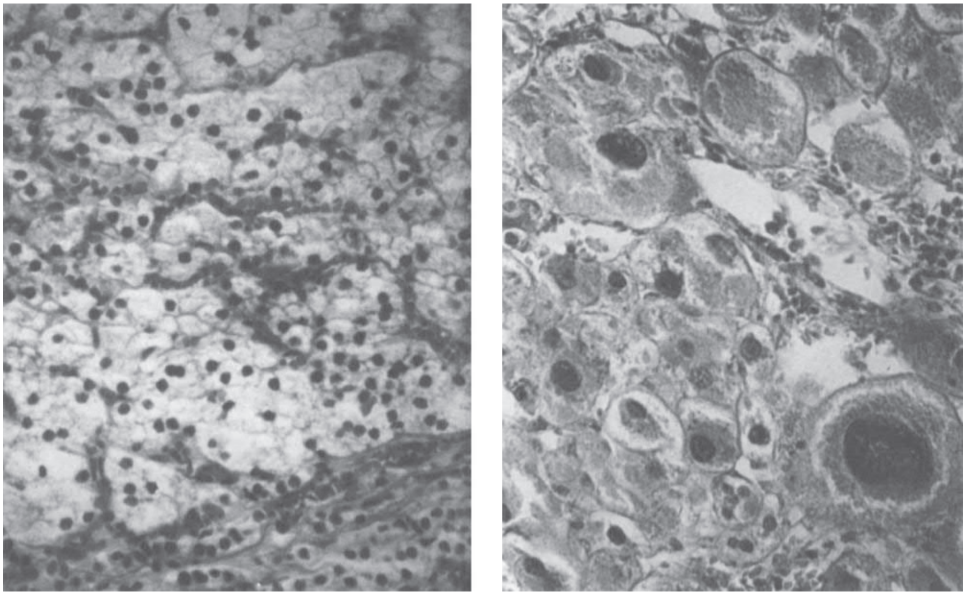
The cortisol excess also suppresses the immune mechanisms, rendering patients susceptible to infection. Inhibition of fibroblast function by excess cortisol further interferes with wound healing.

Hypertension is present in 90% of cases. Although the aldosterone level rately is elevated, cortisol itself exerts a hypertensive effect when present in excessive amounts, as does 11-deoxycorticosterone. The hypertension may be accompanied by manifestation of mineralocorticoid excess (hypokalemia and alkalosis), especially in patients with ectopic ACTH syndrome or adrenocortical carcinoma.

Pathology

The cells in adrenal hyperplasia resemble those of the zona fasciculata of the normal adrenal cortex. Frank adenocarcinoma reveals pleomorphism and invasion of the capsule, the vascular system, or both (Figure 31–2). Local invasion may occur, and metastases are common to the liver, lungs, bone, or brain. Histologic differentiation between adenoma and adenocarcinoma is frequently difficult.

In the presence of adenoma or malignant tumor, atrophy of the cortices of both adrenals occurs because the main secretory product of the tumor is cortisol, which inhibits the pituitary secretion of ACTH. Thus, although the tumor continues to grow, the contralateral adrenal cortex undergoes atrophy.



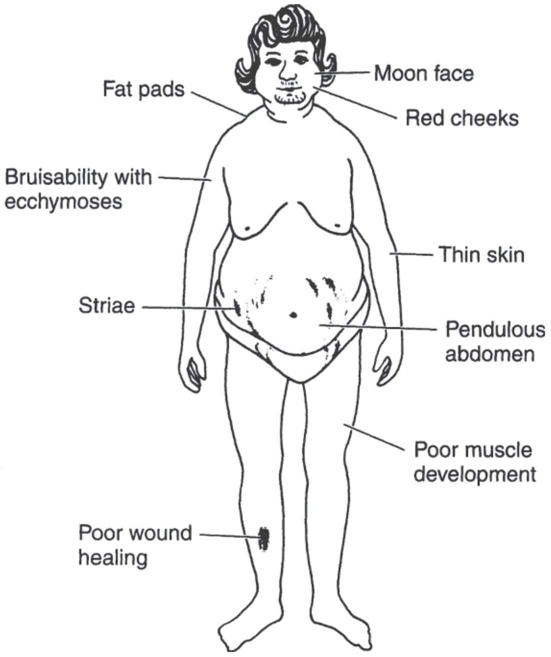
▲ **Figure 31–2.** Adrenal hyperplasia on the left and adrenocortical carcinoma on the right.

Clinical Findings

A. Symptoms and Signs (Figures 31–3 and 31–4)

The clinical presentation of Cushing's syndrome varies, in part related to the extent and duration of cortisol excess. While some symptoms are unmistakable, such as proximal muscle weakness, wasting of the extremities with increased abdominal fat, and wide purple striae, most of the signs and symptoms of Cushing's syndrome are common in the general population. The Endocrine Society Guidelines recommend testing in the following groups:

1. Patients with unusual features for age (eg, osteoporosis, hypertension, type 2 diabetes, thin skin)
2. Patients with multiple and progressive features, particularly those that are more predictive of Cushing's syndrome:
   Easy bruising
   Facial plethora
   Striae (especially if reddish purple and >1 cm wide)
   Proximal myopathy (proximal muscle weakness)
   Weight gain in children with decreased growth velocity
   Obesity
   Dorsocervical fat pad (buffalo hump)
   Decreased concentration or libido
   Depression
   Facial fullness
   Acne
   Hirsutism or female balding
   Insomnia
3. Children with decreasing height percentile and increasing weight
4. Patients with adrenal incidentaloma compatible with adenoma



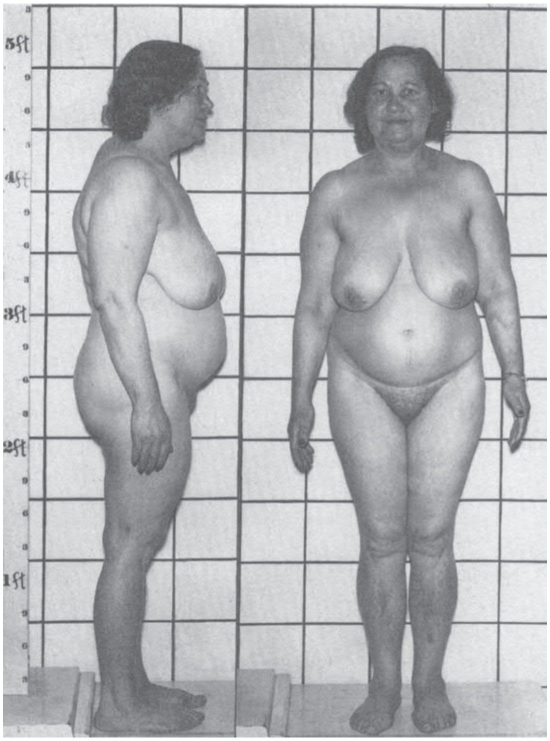
▲ **Figure 31–3.** Cushing's syndrome clinical signs.

B. Laboratory Findings

A thorough drug history should be performed to exclude exogenous glucocorticoid exposure prior to conducting biochemical testing.

1. Recommended testing for Cushing's syndrome—Using two of the three following tests is recommended for initial Cushing's syndrome screening, based on patient suitability. The low-dose dexamethasone test is preferred by the AUA because of its simplicity and higher sensitivity when compared to urine-free cortisol.

A. Overnight dexamethasone suppression test (1 mg)—Dexamethasone in low doses is used to assess the feedback suppression of ACTH and cortisol production by glucocorticoids. Dexamethasone is given at 11 pm and serum



▲ **Figure 31–4.** Cushing's syndrome clinical signs.

cortisol is measured between 8 and 9 am the next morning. ACTH is suppressed in normal persons but not in those with Cushing's syndrome. A lower cutoff for suppression of cortisol to < 1.8 μg/dL (50 nmol/L) is now recommended to achieve greater sensitivity.

Women taking birth control pills have high plasma cortisol levels because, as in pregnancy, the estrogen stimulates production of cortisol-binding globulin. The pills must be withheld for 6 weeks before the dexamethasone suppression test. Other conditions causing false-positive responses are acute illness, depression, and alcoholism.

B. 24-Hour Urine-Free Cortisol (UFC)—This test provides an integrated assessment of cortisol secretion over a 24-hour period and is not affected by conditions and medications that alter serum cortisol level. Since several different assay techniques exist, it is recommended to use the upper limit of normal for the specific assay as cutoff for a positive test. More than one UFC measurement is needed to avoid false-negative results and to detect cyclic hypercortisolism as patients with Cushing's disease may have variable UFC.

C. Late-night salivary cortisol—Serum and salivary cortisol normally peak in the morning and reach a nadir around midnight during sleep. Patients with Cushing's syndrome lose this diurnal nadir, and cortisol levels will be abnormally increased at bedtime. When an ELISA assay is used, normal subjects have salivary cortisol levels of <145 ng/dL (4nmol/liter) at bedtime. The accuracy of this test is reported as being similar to UFC. Salivary cortisol allows the convenience of at home testing, although this test may provide false-positive results in patients with hypertension and diabetes.

2. Specific tests for differentiation of causes of Cushing's syndrome—The various causes of Cushing's syndrome can be determined with great accuracy (95% of cases).

A. Plasma ACTH level—If the diagnosis of Cushing's syndrome has been established, this test will differentiate ACTH-dependent causes (Cushing's disease and the ectopic ACTH syndrome) from adrenal tumors, which are ACTH-independent. The normal range is 10–50 pg/mL. Patients with Cushing's disease have ACTH levels that range from 10 to 200 pg/mL; in the ectopic ACTH syndrome, levels are usually >200 pg/mL, and patients with adrenal tumors have suppressed ACTH levels (<5 pg/mL).

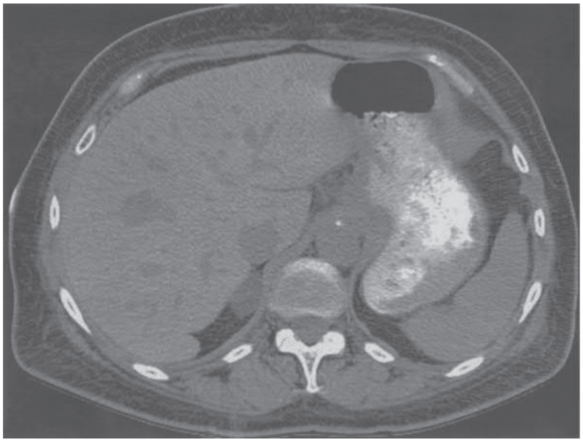
B. Longer low-dose dexamethasone suppression test (2 mg/day for 48 hours)—The basis of this test is to aid in differentiating Cushing's syndrome from Cushing's disease. ACTH secretion in patients with Cushing's disease is not completely, but only partially, resistant to glucocorticoid feedback. Therefore, if the dexamethasone dose is increased, pituitary section of ACTH is suppressed in patients with Cushing's disease, and glucocorticoid production is reduced. In contrast, dexamethasone has no effect in patients with adrenal tumors and ectopic ACTH production, since their pituitary glands are already suppressed.

C. Plasma androgen levels—In patients with adrenal adenomas, androgen levels are normal or low, and in adrenocortical carcinoma, these levels are often markedly elevated.

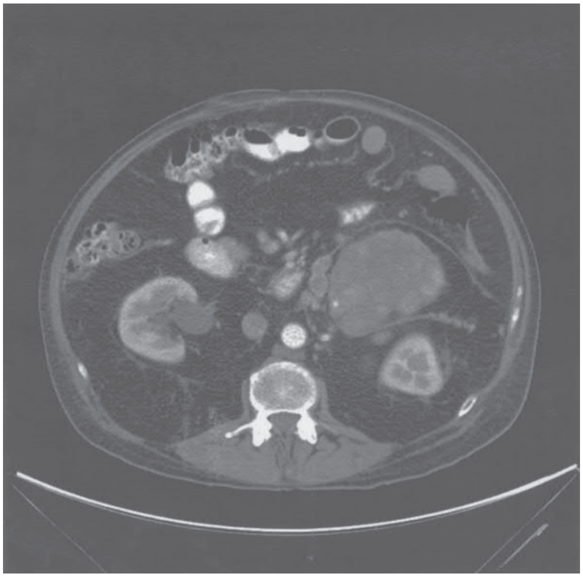
C. X-Ray Findings and Special Examinations

1. Localization of source of ACTH excess—When tests suggest Cushing's disease or the ectopic ACTH syndrome and an elevated plasma level of ACTH is present, the source of ACTH must be identified. Because the great majority of these patients have Cushing's disease and because most of the patients with ectopic ACTH secretion have an obvious malignancy, the first step is to perform **pituitary MRIs.** These are positive in 50–60% of patients with Cushing's disease; in the remainder, the diagnosis should be established by the sampling of ACTH levels in the venous drainage of the anterior pituitary, that is, the cavernous sinuses and inferior petrosal sinuses. If the MRI and venous sampling do not reveal a pituitary source of ACTH, CT scans of the chest and abdomen are used to localize an ectopic tumor.

2. Localization of adrenal lesions—Patients with Cushing's syndrome with suspected adrenal tumors and suppressed ACTH levels should undergo a CT scan of the abdomen with 3-mm sections through the adrenals. Adrenal tumors causing Cushing's syndrome are usually >3 cm in diameter (Figure 31–5) and are therefore easily visualized. Adenomas are usually 3–6 cm in diameter; carcinomas are usually >6 cm in diameter (Figure 31–6) and are frequently locally invasive or metastatic to the liver and lungs at the time of diagnosis. In patients with adrenal tumors, the contralateral adrenal is suppressed and therefore appears atrophic or normal on CT scan. The finding of bilateral adrenal enlargement is typical of Cushing's disease or the ectopic ACTH syndrome. Ultrasound or MRI may also



▲ **Figure 31–5.** Right adrenal tumor.



▲ **Figure 31–6.** Left adrenal carcinoma.

be used for adrenal localization, although these techniques do not appear to offer significant advantage over CT.

Treatment

A. Cushing's Disease

A pituitary microadenoma, which is the most common cause of bilateral adrenocortical hyperplasia, must be located and removed surgically. **Transsphenoidal resection** performed by an experienced neurosurgeon is the method of choice. Success is reported in >80% of cases, and in most instances, the endocrine functions of the pituitary gland are preserved. Pituitary radiation is usually reserved for individuals who cannot undergo surgery or as a second-line treatment when surgery fails.

B. Ectopic ACTH Syndrome

The treatment of these patients is difficult because most have an advanced malignancy and severe hypercortisolism. Removal of the primary tumor is clearly the therapy of choice; however, curative resection is limited to the few patients with benign tumors such as bronchial carcinoids. Patients with residual or metastatic tumors should be managed first with adrenal inhibitors, and if that is not successful, bilateral adrenalectomy should be considered.

C. Total Bilateral Adrenalectomy

Total bilateral adrenalectomy is indicated in patients with Cushing's disease in whom the pituitary tumor is not resectable and in whom medical therapy fails to control the cortisol excess. A laparoscopic approach to adrenalectomy is preferred, since it significantly decreases morbidity and length of hospital stay compared with open adrenalectomy. Bilateral adrenalectomy is also indicated in patients with ectopic ACTH syndrome who have life-threatening hypercortisolism that cannot be controlled by inhibitors of adrenal secretion and premenopausal woman who desire pregnancy soon after correction of Cushing's syndrome.

1. Preoperative preparation—Because removal of the source of excessive cortisol will inevitably lead to temporary or permanent adrenal insufficiency, it is of the utmost importance to administer cortisol preoperatively and to continue substitution therapy after surgery to control Addison's disease.

2. Postoperative status—Many patients suffer from glucocorticoid withdrawal despite the use of physiological replacement. Some practitioners prescribe high doses of glucocorticoid in excess of the usual daily output of approximately 20 mg, as this may improve symptoms. It is important to reduce the steroid substitution gradually over a period of several days. There are various tapering strategies, none of which has been systematically studied. The Endocrine Society recommends glucocorticoid replacement with hydrocortisone, 10–12 mg/m^2 daily in divided doses, either 2 or 3 times daily, with the first dose taken shortly after waking.

D. Adrenal Adenoma and Adenocarcinoma

The majority of all adrenal adenomas and smaller adrenal carcinomas are removed laparoscopically, again allowing decreased hospitalization and more rapid recovery from surgery. There is emerging evidence that robot-assisted adrenalectomy is safe and feasible with a potential to improve outcomes and decrease hospital stay. Unilateral adrenalectomy performed by experienced surgeons is curative in nearly 100% of adults and children, with cortisol producing adrenal adenomas. Adrenal carcinomas that are large, are locally invasive, or involve the inferior vena cava are best approached by an open operation.

1. Preoperative preparation—Preoperative preparation is the same as that for bilateral hyperplasia, since, in this case, the remaining adrenal gland will be atrophic and thus the patient will be hypoadrenal.

2. Postoperative treatment and follow-up—Hydrocortisone is administered preoperatively at doses described earlier with a goal replacement dose of 10–12 mg/m^2 daily. Substitution therapy may be necessary for 6 months to 2 years depending on the rate of recovery of the residual gland. Mineralocorticoid therapy is rarely necessary, since the atrophic adrenal usually produces a sufficient amount of aldosterone. Patients with adrenocortical carcinoma are usually not cured by surgery and require additional therapy.

E. Medical Therapy

Medical therapy is indicated in patients who either cannot undergo surgery (eg, because of debility, recent myocardial infarction) or have had unsuccessful resection of their pituitary, ectopic, or adrenal tumor. Medications aimed to restore eucortisol levels fall under one of three general categories: steroidogenesis inhibitors, pituitary-directed, and glucocorticoid receptor-directed.

1. Steroidogenesis inhibitors

A. Ketoconazole—This drug blocks adrenal and gonadal steroid secretion by inhibiting P450c11 and P450scc, reducing UFC by approximately 50% in majority of Cushing's disease patients. The total dose required is 400–1600 mg daily divided into three or four doses. Side effects include adrenal insufficiency, abnormal liver function tests, and rarely hepatotoxicity.

B. Metyrapone—This drug inhibits 11-β-hydroxylase and controls hypercortisolism in approximately 50–75% of patients. It may be administered alone or concurrently with ketoconazole. The usual dosage ranges from 500 mg to 6 g daily, given in three to four divided doses. Side effects include GI upset, hypertension, hirsutism, and hypokalemia.

C. Mitotane—This drug is both an inhibitor of adrenal secretion and a cytotoxic agent that damages adrenocortical cells. Mitotane is not used as monotherapy, yet almost exclusively as adjuvant therapy in patients with residual adrenocortical carcinoma. The usual dosage ranges from 500 mg to 8 g daily in three to four divided doses. Side effects, including GI upset, gynecomastia, leukopenia, and depression lead to discontinuation in nearly 28% of patients.

Mitotane is US FDA-approved for treating adrenal cancer. Ketoconazole and metyrapone are approved only in Europe for the treatment of hypercortisolism.

2. Pituitary-directed agents—Cabergoline and pasireotide act directly on pituitary tumors to halt ACTH production. They are not effective in treating adrenal sources of hypercortisolism.

A. Cabergoline—This drug, a dopamine agonist, is effective in nearly 40% of patients with pituitary adenomas. Adverse effects include asthenia and GI upset. Usual dosage is 1–7 mg weekly.

B. Pasireotide—This drug, a somatostatin receptor agonist, normalizes UFC levels in approximately 20% of patients who failed surgery. Dosing is 600–900 μg twice daily.

3. Glucocorticoid receptor—directed agents

A. Mifepristone—This drug is a glucocorticoid receptor antagonist and antiprogestin approved in the United States for the control of diabetes secondary to hypercortisolism in patients who failed or cannot undergo surgery. Cortisol levels remain stable or may increase during treatment, which can make dosing difficult. Starting dose is 300 mg daily followed by slow clinical titration. Adverse effects include headaches, GI upset, hypertension, and arthralgias.

▶ Prognosis

Treatment of hypercortisolism usually leads to disappearance of symptoms and many signs within days to weeks, but osteoporosis usually persists in adults, whereas hypertension and diabetes often improve. Cushing's disease treated by pituitary adenomectomy has an excellent early prognosis, and long-term follow-up shows a recurrence rate of about 10%. Patients with the ectopic ACTH syndrome and malignant tumors in general have a poor prognosis. Patients with benign lesions may be cured by resection of the tumor. Removal of an adrenal adenoma offers an excellent prognosis, and these patients are cured by unilateral adrenalectomy.

The outlook for patients with adrenocortical carcinoma is poor. The antineoplastic drug mitotane reduces the symptoms and signs of Cushing's syndrome but does little to prolong survival. Radiotherapy and chemotherapy are not successful in these patients.

ADRENAL ANDROGENIC SYNDROMES

Adrenal androgenic syndromes result from the abnormal production of sex steroids and are more common in females. Congenital bilateral adrenal hyperplasia and tumors, both benign and malignant, may be observed. In contrast to Cushing's syndrome, which is protein-catabolic, the androgenic syndromes are anabolic. In untreated cases, there is a marked recession of the hairline, increased beard growth, and excessive growth of pubic and sexual hair, in general, in both sexes. In males, there is enlargement of the penis, usually with atrophic testes; in females, enlargement of the clitoris occurs, with atrophy of the breasts and amenorrhea. Muscle mass increases and fat content decreases, leading to a powerful but trim figure. The voice becomes deeper, particularly in females; this condition is irreversible, because it is due to enlargement of the larynx. In both sexes, there may be increased physical sexual aggressiveness and libido.

▶ Congenital Bilateral Adrenal Androgenic Hyperplasia (CAH)

A. Pathophysiology

An autosomal recessive defect in certain adrenal enzymes results in glucocorticoid deficiency and subsequent androgen excess, causing a **disorder of sexual differentiation (DSD)** in females and **macrogenitosomia** in males. CAH is the most common cause of adrenal insufficiency in the pediatric population and is associated with excess androgen production in utero. In females, the Müllerian duct structures (eg, ovaries, uterus, vagina) develop normally, but the excess androgen exerts a masculinizing effect on the urogenital sinus and genital tubercle, so that the vagina is connected to the urethra, which, in turn, opens at the base of the enlarged clitoris. The labia are often hypertrophied. Externally, the appearance is that of severe hypospadias with cryptorchidism.

The adrenal cortex secretes mostly anabolic and androgenic steroids, leading to various degrees of cortisol deficiency depending on the nature of the enzyme block. This increases the secretion of ACTH, which causes hyperplasia of both adrenal cortices and diversion of accumulated cortisol precursors to androgenic steroid synthesis. 21-Hydroxylase deficiency, which accounts for approximately 95% of CAH, does not allow for the transformation of 17α-hydroxyprogesterone to cortisol, or of progesterone to aldosterone. This common deficiency occurs in two forms: the classic salt-losing variety, with low-to-absent aldosterone, and the less frequent non–salt-losing type.

B. Clinical Findings

1. Clinical symptoms and signs—Infants may be asymptomatic with mild androgen excess, or present with life-threatening adrenal insufficiency and DSD, depending on the type and disease severity. In newborn girls, the appearance of the external genitalia resembles severe hypospadias with cryptorchidism. Infant boys may appear normal at birth, making diagnosis more difficult. Many countries, including the United States, have implemented newborn screening for 21-hydroxylase deficiency. Older children may develop pseudo precocious puberty and accelerated growth and skeletal maturation.

In untreated cases, hirsutism, excess muscle mass, and, eventually, amenorrhea is the rule. Breast development is poor. In males, growth of the phallus is excessive. The testes are often atrophic because of inhibition of gonadotropin secretion by the elevated androgens. On rare occasions, hyperplastic adrenocortical rests in the testes make them large and firm. In most instances, there is azoospermia after puberty.

2. Growth rate—In both males and females with androgenic hyperplasia, the growth rate is initially increased so that they are taller than their classmates. At about age 9–10 years, premature fusion of the epiphyses caused by excess androgen causes termination of growth so that these patients are short as adults.

C. Laboratory Findings

Urinary 17-ketosteroid levels are higher than normal for sex and age, and plasma 21-deoxycortisol, androstenedione, DHEA, DHEA-S, and testosterone levels are elevated. Plasma ACTH is also elevated, and in patients with the most common defect (ie, 21-hydroxylase deficiency), plasma 17α-hydroxyprogesterone is markedly elevated. Chromosome studies are normal.

D. X-Ray Findings

X-rays show acceleration of bone age.

E. CT Scans

Scans usually show the hypertrophied adrenals.

Treatment

It is imperative to make the diagnosis early. Treatment of the underlying cause is medical, with the goal of suppressing excessive ACTH secretion, thus minimizing excess androgenicity. This is accomplished by adrenal replacement with glucocorticoids in doses sufficient to suppress adrenal androgen production and therefore prevent virilization and rapid skeletal growth. The Endocrine Society recommends hydrocortisone tablets for children because this ensures fewer adverse growth effects and reservation of prednisone and dexamethasone for nongrowing patients. In patients with mineralocorticoid deficiency, fludrocortisone (0.05–0.2 mg, depending on severity and age) together with sodium chloride supplements is necessary to stabilize blood pressure and body weight.

The vagina can be surgically separated from the urethra and opened in the normal position on the perineum during early infancy or after puberty; however, controversy exists on the ideal timing of reconstruction. Judicious administration of estrogens or birth control pills feminizes patients.

Prognosis

If the condition is recognized early and ACTH suppression is begun even before surgical repair of the genital anomaly, the outlook for normal linear growth and development is excellent. The prevalence of hypertension, obesity, and future infertility is increased secondary to excess glucocorticoid exposure. In some female patients, menses begins after treatment, and conception and childbirth can occur when the anatomic abnormalities are minimal or have been surgically repaired.

Adrenocortical tumors producing androgens are most frequently carcinomas; however, a few benign adenomas have been reported. Most of the carcinomas also hypersecrete other hormones (ie, cortisol or 11-deoxycorticosterone), and thus, the clinical presentation is variable. Female patients present with androgen excess, which may be severe enough to cause virilization; many of these patients also have Cushing's syndrome and mineralocorticoid excess (hypertension and hypokalemia). In adult males, excess androgens may cause no clinical manifestations, and diagnosis in these patients may be delayed until there is abdominal pain or an abdominal mass. These patients may also present with Cushing's syndrome and mineralocorticoid excess.

PRIMARY ALDOSTERONISM (CONN'S SYNDROME)

Excessive production of aldosterone, due mostly to aldosteronoma or spontaneous bilateral hyperplasia of the zona glomerulosa of the adrenal cortex, leads to the combination of hypertension, sodium retention, potassium excretion, and nocturia.

Pathophysiology

Excessive aldosterone, acting on most cell membranes in the body, produces typical changes in the distal renal tubule and the small bowel that lead to increased renal sodium reabsorption and hydrogen ion secretion together with urinary potassium loss that, if prolonged and severe, will cause hypokalemia. Contrary to previous beliefs, it is now known that only a minority of patients (9–37%) develop hypokalemia. Sodium retention leads to plasma volume expansion, elevated blood pressure, and cardiovascular damage. Plasma renin and, secondarily, plasma angiotensin, are depressed by excess aldosterone as a result of blood volume expansion. A syndrome resembling nephrogenic diabetes insipidus may occur as a result of reversible damage to the renal collecting tubules.

Clinical Findings

A. Symptoms and Signs

Normokalemic hypertension is usually the presenting manifestation, with accompanying hypokalemia likely present in the most severe cases. Headaches are common, nocturia is invariably present, and rare episodes of paralysis occur with very low serum potassium levels. Numbness and tingling of the extremities are related to alkalosis and may lead to tetany if severe.

B. Laboratory Findings

Before screening tests are undertaken, one must ascertain that the patient is not taking oral contraceptives or other estrogen preparations, since these may increase renin and angiotensin levels and therefore aldosterone levels, thus raising the blood pressure artificially. Withdrawal of these medications for 1 week is mandatory. Diuretics must also be discontinued, since they lower blood volume and induce secondary aldosteronism and hypokalemia.

In true aldosterone excess, serum sodium is slightly elevated and CO_2 is increased, whereas serum potassium may be normal or low. Definitive diagnosis rests on demonstration of an elevated plasma aldosterone/renin ration (ARR). Because of the lack of consensus on assay protocols, it is recommended that patients with an elevated plasma AAR undergo confirmation testing such as an oral sodium loading test or saline infusion test. However, in patients who have an elevated AAR and spontaneous hypokalemia, further diagnostic testing is not warranted.

Secondary hyperaldosteronism may accompany renovascular hypertension. This, too, may be associated with hypokalemic alkalosis; however, the renin level is elevated rather than suppressed. Essential hypertension does not cause changes in the electrolyte pattern. Definitive tests for hyperaldosteronism show negative results.

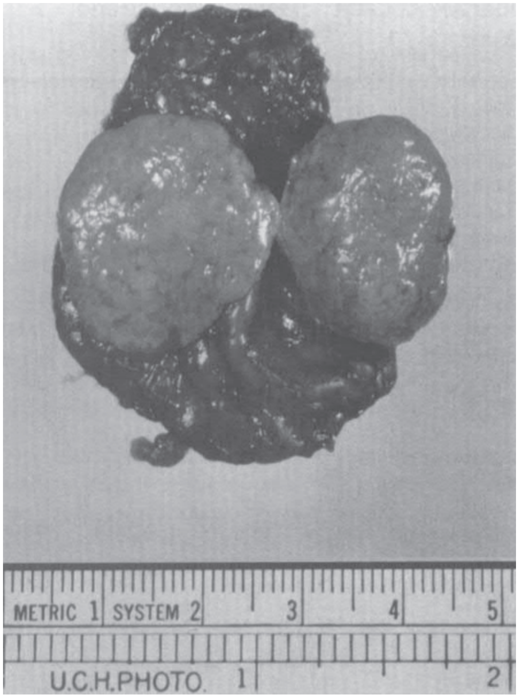
C. Localization

A thin-section CT scan is the initial procedure and will localize an adenoma in most patients (Figure 31–9). However, CT imaging cannot reliably differentiate adrenal microadenomas, nonfunctioning incidentalomas, aldosterone-producing adenomas, and certain other adrenal tumors (eg, see Figures 31–8 through 31–10). Therefore, if surgical treatment is being considered, adrenal vein sampling should be performed to distinguish unilateral from bilateral forms of primary aldosteronism.

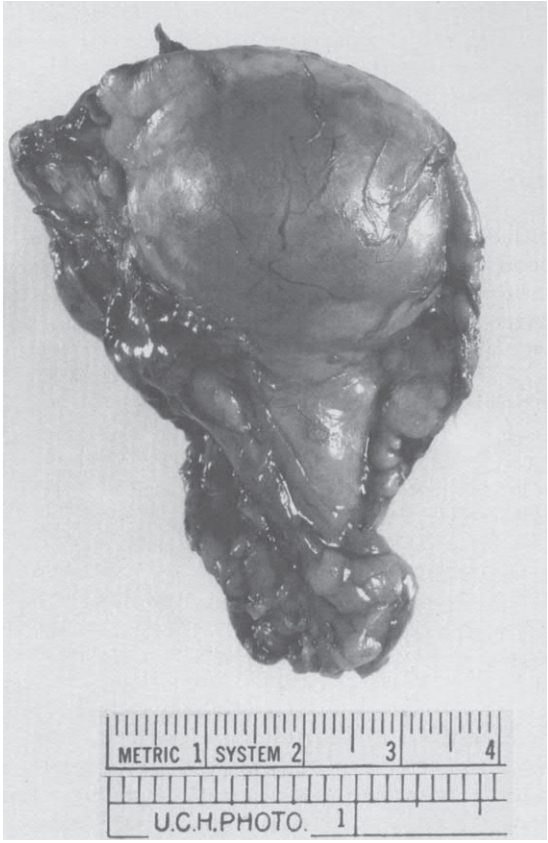
Treatment

A. Aldosteronoma

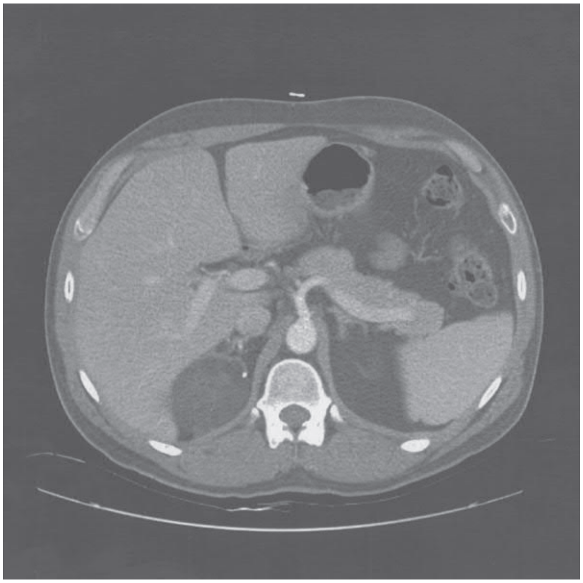
If the site of the tumor has been established, only the affected adrenal need be removed. Again, the procedure of choice is laparoscopic unilateral adrenalectomy, which is highly successful at resolving the metabolic defect.



▲ **Figure 31–7.** Gross view of resected aldosteronoma.



▲ **Figure 31–8.** Gross view of resected adrenal adenoma.



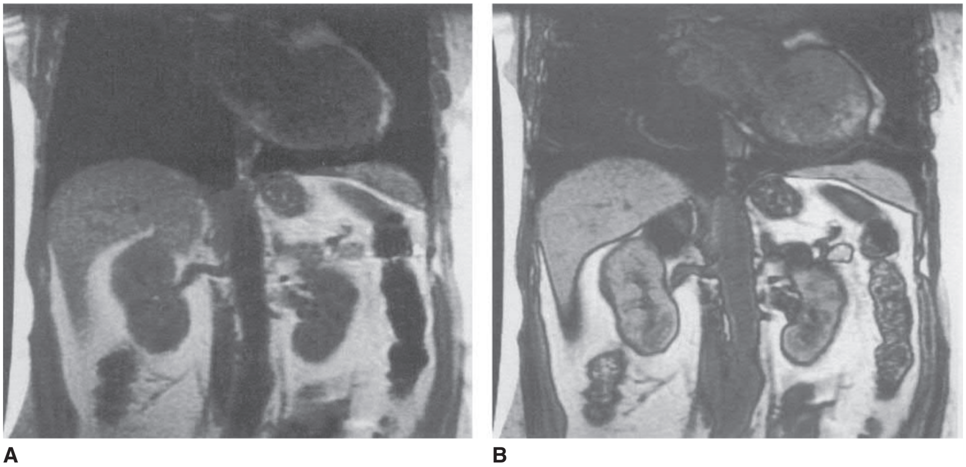
▲ **Figure 31–9.** CT contrast view of bilateral adrenal hyperplasia.

B. Bilateral Nodular Hyperplasia

Few authorities recommend resection of both adrenals, since the fall in blood pressure is only temporary and electrolyte imbalance may continue. Medical treatment is recommended.

C. Medical Treatment

If surgery must be postponed, if the hypertension is mild in an older person, or if bilateral hyperplasia is the cause, medical treatment with spironolactone (Aldactone), 12.5–25 mg



▲ **Figure 31–10.** MRI of coronal sections of right adrenal adenoma.

orally once daily, is recommended. Eplerenone is an alternative mineralocorticoid receptor antagonist with greater selectivity yet less potency. Amiloride, a potassium-sparing diuretic, may be given in doses of up to 20–40 mg/day. Other antihypertensive agents may also be necessary.

Prognosis

Following removal of an adrenal adenoma, the hypokalemia resolves. Fifty percent of patients become normotensive without assistance of antihypertensive drugs. Bilateral nodular hyperplasia is not amenable to surgical treatment, and the results of medical treatment are variable.

BIBLIOGRAPHY

General

Autorino R et al: Open versus laparoscopic adrenalectomy for adrenocortical carcinoma: A meta-analysis of surgical and oncologic outcomes. Ann Surg Oncol 2016;23:1195–1202.

Bovio S et al: Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. J Endocrinol Invest 2006; 29:298–302.

Brandao LF et al: Robot-assisted laparoscopic adrenalectomy: Step-by-step technique and comparative outcomes. Eur Urol 2014;66:898–905.

Mir MC et al: Comparative outcomes of laparoscopic and open adrenalectomy for adrenocortical carcinoma: Single, high-volume center experience. Ann Surg Oncol 2013;20:1456–1461.

Osswald A et al: Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. Eur J Endocrinol 2014; 171: 209–215.

Park HS et al: Outcomes from 3144 adrenalectomies in the United States: Which matters more, surgeon volume or specialty? Arch Surg 2009;144:1060–1067.

Pena CS et al: Characterization of indeterminate (lipid-poor) adrenal masses: Use of washout characteristics at contrast-enhanced CT. Radiology 2000;217:798–802.

Smith CD et al: Laparoscopic adrenalectomy: New gold standard. World J Surg 1999;23:389.

Swearingen B: Update on pituitary surgery. J Clin Endocrinol Metab 2012;97:1073–1081.

Incidentaloma

Mandeveille J, Moinzadeh A: Adrenal ncidentalomas. Lesson 4, AUA Update Series 2010;29:34–39.

Nieman LK: Approach to the patient with an adrenal incidentaloma. J Clin Endocrinol Metab 2010;95(9):4106–4113.

NIH. NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("indidentaloma"). NIH Consensus State Sci Statements 2002;19:1–25.

Pantalone KM et al: Change in adrenal mass size as a predictor of a malignant tumor. Endocr Pract 2010;16:577–587.

Young WF Jr: Clinical practice: The incidentally discovered adrenal mass. New Engl J Med 2007;356:601–610.

Zeiger MA et al: American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the management of adrenal incidentalomas: Executive summary of recommendations. Endocr Pract 2009; 15:450–453.

Cushing's Syndrome and Adrenocortical Tumors

Atkinson AB: The treatment of Cushing's syndrome. Clin Endocrinol (Oxford) 1991;34:507.

Azoury SC et al: Computed tomography in the management of adrenal tumors: Does size still matter? J Comput Assist Tomogr 2017;41:628–632.

Boushey RP, Dackiw AP: Adrenal cortical carcinoma. Curr Treat Options Oncol 2001;2:355.

Colao A et al: A 12-month phase 3 study of pasireotide in Cushing's disease. New Engl J Med 2012;366:914–924.

Decker RA et al: Eastern Cooperative Oncology Group Study 1879: Mitotane and adriamycin in patients with advanced adrenocortical carcinoma. Surgery 1991;110:1006.

Doherty GM et al: Time to recovery of the hypothalamic-pituitary-adrenal axis after curative resection of adrenal tumors in patients with Cushing's syndrome. Surgery 1990;108:1085.

Elamin MB et al: Accuracy of diagnostic tests for Cushing syndrome: A systematic review and meta-analyses. J Clin Endocrinol Metab 2008;93:1553–1562.

Feelders RA et al: Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. New Engl J Med 2010;362:1846–1848.

Findling JW, Raff H: Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am 2001;30:729.

Fleseriu M et al: A new therapeutic approach in the medical treatment of Cushing's syndrome: Glucocorticoid receptor blockade with mifepristone. Endocr Pract 2013;19:313–326.

Grossman A et al: Therapy of endocrine disease: Perspectives on the management of adrenal insufficiency: Clinical insights from across Europe. Eur J Endocrinol 2013;169:165–175.

Grus JR, Nelson DH: ACTH-producing pituitary tumors. Endocrinol Metab Clin North Am 1991;20:319.

Lacroix A et al: Cushing's syndrome. Lancet 2015;386:913–927.

Luton JP et al: Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. New Engl J Med 1990;322:1195.

Mandeveille J, Moinzadeh A: Adrenal incidentalomas. AUA Update Series, Lesson 4, 2010;29:34–39.

Mendiratta-Lala M et al: Efficacy of radiofrequency ablation in the treatment of small functional adrenal neoplasms. Radiology 2010; 258(1):308–316.

Ng L, Libertino JM: Adrenocortical carcinoma diagnosis, evaluation and treatment. J Urol 2003;169:5.

Nieman LK et al: The diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93(5):1526–1540.

Nieman LK et al: Treatment of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100:2807–2831.

Nieman LK: Cushing's Syndrome: Update on signs, symptoms and biochemical screening. Eur J Endocrinol 2015;173:33–38.

Raff H, Findling, JW: A physiologic approach to diagnosis of the Cushing syndrome. Ann Intern Med 2003;138:980.

Stratakis CA: Cushing syndrome in pediatrics. Endocrinol Metab Clin North Am 2012;41:793–803.

Styne DM et al: Treatment of Cushing's disease in childhood and adolescence by transsphenoidal microadenomectomy. New Engl J Med 1984;B310:889.

Trainer PJ, Grossman A: The diagnosis and differential diagnosis of Cushing's syndrome. Clin Endocrinol (Oxford) 1991;34:317.

Tyrrell JB et al: An overnight high-dose dexamethasone suppression test: Rapid differential diagnosis of Cushing's syndrome. Ann Intern Med 1986;104:180.

Adrenal Androgenic Syndromes

Abiven G et al: Clinical and biological features in the prognosis of adrenocortical cancer: Poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab 2006;91:2650–2655.

Else T et al: Adrenocortical carcinoma 2014;35:282–326.

Krone N, Hanley NA, Arlt W: Age-specific changes in sex steroid biosynthesis and sex development. Best Pract Res Clin Endocrinol Metab 2007;21:393–401.

Siegel SF et al: ACTH stimulation tests and plasma dehydroepiandrosterone sulfate levels in women with hirsutism. New Engl J Med 1990;323:849.

Speiser PW et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endorcrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2010;95:4133–4160.

Webb EA et al: Current and novel approaches to children and young people with congenial and renal hyperplasia and adrenal insufficiency. Best Practice Res Clinical Endocrinol Metab 2015;29: 449–468.

White PC: Optimizing newborn screening for congenital adrenal hyperplasia. J Pediatr 2013;163:10–12.

Primary Aldosteronism

Conn JW et al: Normokalemic primary aldosteronism. A detectable cause of curable "essential" hypertension. JAMA 1965;193: 200–206.

Funder JW et al: The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101:1889–1916.

Ganguly A: Primary aldosteronism. New Engl J Med 1998;339:1828.

Gomez-Sanchez CE: Primary aldosteronism and its variants. Cardiovasc Res 1998;37:8.

Gordon RD: Primary aldosteronism. J Endocrinol Invest 1995; 18:495.

Parthasarathy HK et al: A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens 2011;29:980–990.

Rossi GP et al: A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 2006; 48:2293–2300.

Rossi GP et al: Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. Hypertension 2013;62:62–69.

Rossi GP et al: The adrenal vein sampling international study (AVIS) for identifying the major subtypes of primary aldosteronism. J Clin Endocrinol Metab 2012;97:1606–1614.

Shen WT et al: Laparoscopic vs open adrenalectomy for the treatment of primary hyperaldosteronism. Arch Surg 1999;134:628.

Siren J et al: Laparoscopic adrenalectomy for primary aldosteronism. Surg Laparosc Endosc 1999;9:9.

Sukor N et al: Improved quality of life, blood pressure, and biochemical status following laparoscopic adrenalectomy for unilateral primary aldosternism. J Clin Endocrinol Metab 2010;95: 1360–1364.

Vallotton MB: Primary aldosteronism. Part I. Diagnosis of primary hyperaldosteronism. Clin Endocinol (Oxford) 1996;45:47.

Vallotton MB: Primary aldosteronism. Part II. Differential diagnosis of primary hyperaldosteronism and pseudoaldosteronism. Clin Endocrinol (Oxford) 1996;45:53.

Young WF Jr et al: Primary aldosteronism: Adrenal venous sampling. Surgery 1996;120:913.

Disorders of the Kidneys

32

David B. Bayne, MD, MPH;
Jack W. McAninch, MD, FACS, FRCS(E)(Hon);
& Thomas Chi, MD

CONGENITAL ANOMALIES OF THE KIDNEYS

Congenital anomalies occur more frequently in the kidney than in any other organ. Some cause no difficulty, but many (eg, hypoplasia, polycystic kidneys) cause impairment of renal function. It has been noted that children with a gross deformity of an external ear associated with ipsilateral maldevelopment of the facial bones are apt to have a congenital abnormality of the kidney (eg, ectopy, hypoplasia) on the same side as the visible deformity. Lateral displacement of the nipples has been observed in association with bilateral renal hypoplasia.

A significant incidence of renal agenesis, ectopy, malrotation, and duplication has been observed in association with congenital scoliosis and kyphosis. Unilateral agenesis, hypoplasia, and dysplasia are often seen in association with supralevator imperforate anus. For a better understanding of these congenital abnormalities, see the discussion of the embryology and development of the kidney in Chapter 2.

AGENESIS

Bilateral renal agenesis is extremely rare; no more than 400 cases have been reported, providing an incidence estimate of 0.013% (Thomas and McCullough, 2017). Generally children do not survive this condition, with one exception published where a child survived beyond the neonatal period with serial amnioinfusions starting at 23 weeks' gestation. This allowed the child to survive using peritoneal dialysis after birth as a bridge toward renal transplant at one year of age (Bienstock et al, 2014). The condition does not appear to have any predisposing factors. Prenatal suspicion of the anomaly exists when oligohydramnios is present on fetal ultrasound examination. Pulmonary hypoplasia and facial deformities (Potter facies) are usually present. Abdominal ultrasound examination usually establishes the diagnosis.

One kidney may be absent (estimated incidence 4 in 10,000 births [Laurichesse Delmas et al, 2017]). In some cases, this may be because the ureteral bud (from the Wolffian duct) failed to develop or, if it did develop, did not reach the metanephros (adult kidney). Without a drainage system, the metanephric mass undergoes atrophy. The ureter is absent on the side of the unformed kidney in 50% of cases, although a blind ureteral duct may be found (see Chapter 2).

Renal agenesis causes no symptoms; it is usually found by accident on abdominal or renal imaging. It is not an easy diagnosis to establish even though on inspection of the bladder, the ureteral ridge is absent and no orifice is visualized, for the kidney could be present but be drained by a ureter whose opening is ectopic (into the urethra, seminal vesicle, or vagina). If definitive diagnosis seems essential, isotope studies, ultrasonography, and computed tomography (CT) should establish the diagnosis.

There appears to be an increased incidence of infection, hydronephrosis, and stones in the contralateral organ. Other congenital anomalies associated with this defect include cardiac, vertebral column, and anal anomalies, as well as anomalies of the long bones, hands, and genitalia.

HYPOPLASIA

Hypoplasia implies a small kidney. The total renal mass may be divided in an unequal manner, in which case one kidney is small while the other is correspondingly larger than normal. Some of these congenitally small kidneys prove, on pathologic examination, to be dysplastic. Unilateral or bilateral hypoplasia has been observed in infants with fetal alcohol syndrome, and renal anomalies have been reported in infants with in utero cocaine exposure.

Differentiation from acquired atrophy is difficult. Atrophic pyelonephritis usually reveals typical distortion of the calyces. Vesicoureteral reflux in infants may cause a dwarfed kidney even in the absence of infection. Stenosis of the renal artery leads to shrinkage of the kidney.

Such kidneys have small renal arteries and branches and are associated with hypertension, which is relieved by nephrectomy. Selective renal venography is helpful in differentiating between a congenitally absent kidney and one that is small and nonvisualized.

SUPERNUMERARY KIDNEYS

The presence of a third kidney is very rare; the presence of four separate kidneys in one individual has been reported only 5 times in the literature (Keskin et al, 2014). The anomaly must not be confused with duplication (or triplication) of the renal pelvis in one kidney, which is not uncommon.

DYSPLASIA AND MULTICYSTIC KIDNEY

Renal dysplasia has protean manifestations. Multicystic kidney of the newborn is usually unilateral, nonhereditary, and characterized by an irregularly lobulated mass of cysts; the ureter is usually absent or atresic. It may develop because of faulty union of the nephron and the collecting system. At most, only a few embryonic glomeruli and tubules are observed. The only finding is the discovery of an irregular mass in the flank. Nothing is shown on urography, but in an occasional case, some radiopaque fluid may be noted. If the cystic kidney is large, its mate is usually normal. However, when the cystic organ is small, the contralateral kidney is apt to be abnormal. The cystic nature of the lesion may be revealed by sonography, and the diagnosis can be established in utero. If the physician feels that the proper diagnosis has been made, no treatment is necessary. If there is doubt about the diagnosis, nephrectomy is considered the procedure of choice. Neoplastic changes in multicystic renal dysplasia have been described, but this is accepted as a benign condition. In 300 multicystic dysplastic kidney patients followed over a 30-year period, no malignancy was identified (Eickmeyer et al, 2014).

Multicystic kidney is often associated with contralateral renal and ureteral abnormalities. Contralateral ureteropelvic junction obstruction is one of the common problems noted. Diagnostic evaluation of both kidneys is required to establish the overall status of anomalous development.

Dysplasia of the renal parenchyma is also seen in association with ureteral obstruction or reflux that was probably present early in pregnancy. It is relatively common as a segmental renal lesion involving the upper pole of a duplicated kidney whose ureter is obstructed by a congenital ureterocele. It may also be found in urinary tracts severely obstructed by posterior urethral valves; in this instance, the lesion may be bilateral.

Microscopically, the renal parenchyma is "disorganized." Tubular and glomerular cysts may be noted; these elements are fetal in type. Islands of metaplastic cartilage are often seen. The common denominator seems to be fetal obstruction.

ADULT POLYCYSTIC KIDNEY DISEASE

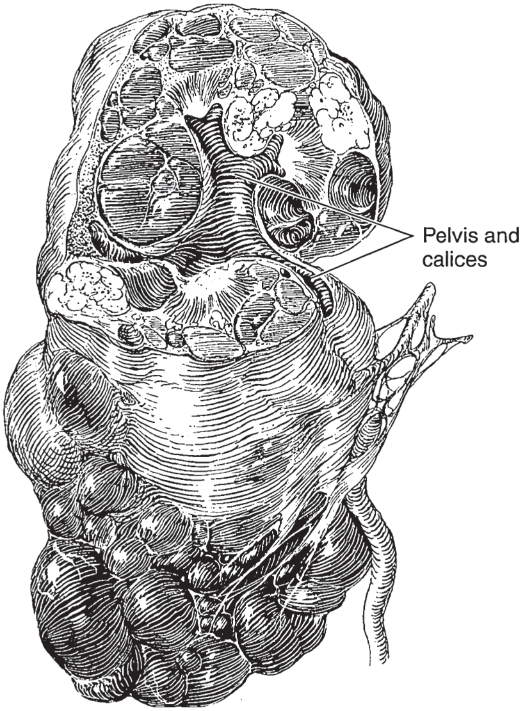
Adult polycystic kidney disease is an autosomal dominant hereditary condition and almost always bilateral (95% of cases). The disease encountered in infants is different from that seen in adults, although the literature reports a small number of infants with the adult type. The former is an autosomal recessive disease in which life expectancy is short, whereas that diagnosed in adulthood is autosomal dominant; symptoms ordinarily do not appear until after age 40 years. Cysts of the liver, spleen, and pancreas may be noted in association with both forms. The kidneys are larger than normal and are studded with cysts of various sizes.

Etiology and Pathogenesis

The evidence suggests that the cysts occur because of defects in development of the collecting and uriniferous tubules and in the mechanism of their joining. Blind secretory tubules that are connected to functioning glomeruli become cystic. As the cysts enlarge, they compress the adjacent parenchyma, destroy it by ischemia, and occlude normal tubules. The result is progressive functional impairment.

Pathology

Grossly, the kidneys are usually significantly enlarged. Their surfaces are studded with cysts of various sizes (Figure 32–1). On section, the cysts are found to be scattered throughout the parenchyma. Calcification is rare. The fluid in the cyst is usually amber-colored but may be hemorrhagic.



▲ **Figure 32–1.** Polycystic kidney. Multiple cysts deep in the parenchyma and on the surface. Note distortion of the calyces by the cysts.

Microscopically, the lining of the cysts consists of a single layer of cells. The renal parenchyma may show peritubular fibrosis and evidence of secondary infection. There appears to be a reduction in the number of glomeruli, some of which may be hyalinized. Renal arteriolar thickening is a prominent finding in adults.

Clinical Findings

A. Symptoms

Pain over one or both kidneys may occur because of the drag on the vascular pedicles by the heavy kidneys, from obstruction or infection, or from hemorrhage into a cyst. Gross or microscopic total hematuria is not uncommon and may be severe; the cause for this is not clear. Colic may occur if blood clots or stones are passed. The patient may notice an abdominal mass.

Infection (chills, fever, renal pain) commonly complicates polycystic disease. Symptoms of vesical irritability may be the first complaint. When renal insufficiency ensues, headache, nausea and vomiting, weakness, and loss of weight occur.

B. Signs

One or both kidneys are usually palpable. They may feel nodular. If infected, they may be tender. Hypertension is found in 60–70% of these patients. Evidence of cardiac enlargement is then noted.

Fever may be present if pyelonephritis exists or if cysts have become infected. In the uremic stage, anemia and loss of weight may be evident. Ophthalmoscopic examination may show changes typical of moderate or severe hypertension.

C. Laboratory Findings

Anemia may be noted, caused either by chronic loss of blood or, more commonly, by the hematopoietic depression accompanying uremia. Proteinuria and microscopic (if not gross) hematuria are the rule. Pyuria and bacteriuria are common.

Progressive loss of the ability to concentrate occurs. Renal clearance tests show varying degrees of renal impairment. About one-third of patients with polycystic kidney disease are uremic when first seen.

D. X-Ray Findings

Both renal shadows are usually enlarged on a plain film of the abdomen, even by as much as 5 times normal size. Kidneys measuring >16 cm in length are suspect.

The renal masses are usually enlarged and the calyceal pattern is quite bizarre (spider deformity). The calyces are broadened and flattened, enlarged, and often curved, as they tend to hug the periphery of adjacent cysts. Often, the changes are only slight or may even be absent on one side, leading to the erroneous diagnosis of tumor of the other kidney. If cysts are infected, perinephritis may obscure the renal and even the psoas shadows.

E. CT Scanning

Computed tomography is an excellent noninvasive technique used to establish the diagnosis of polycystic disease. The multiple thin-walled cysts filled with fluid and the large renal size make this imaging method extremely accurate (95%) for diagnosis.

F. Isotope Studies

Photoscans reveal multiple “cold” avascular spots in large renal shadows.

G. Ultrasonography

Sonography appears to be superior to both excretory urography and isotope scanning in diagnosis of polycystic disorders.

H. Instrumental Examination

Cystoscopy may show evidence of cystitis, in which case the urine will contain abnormal elements. Bleeding from a ureteral orifice may be noted. Ureteral catheterization and retrograde urograms are rarely indicated.

Differential Diagnosis

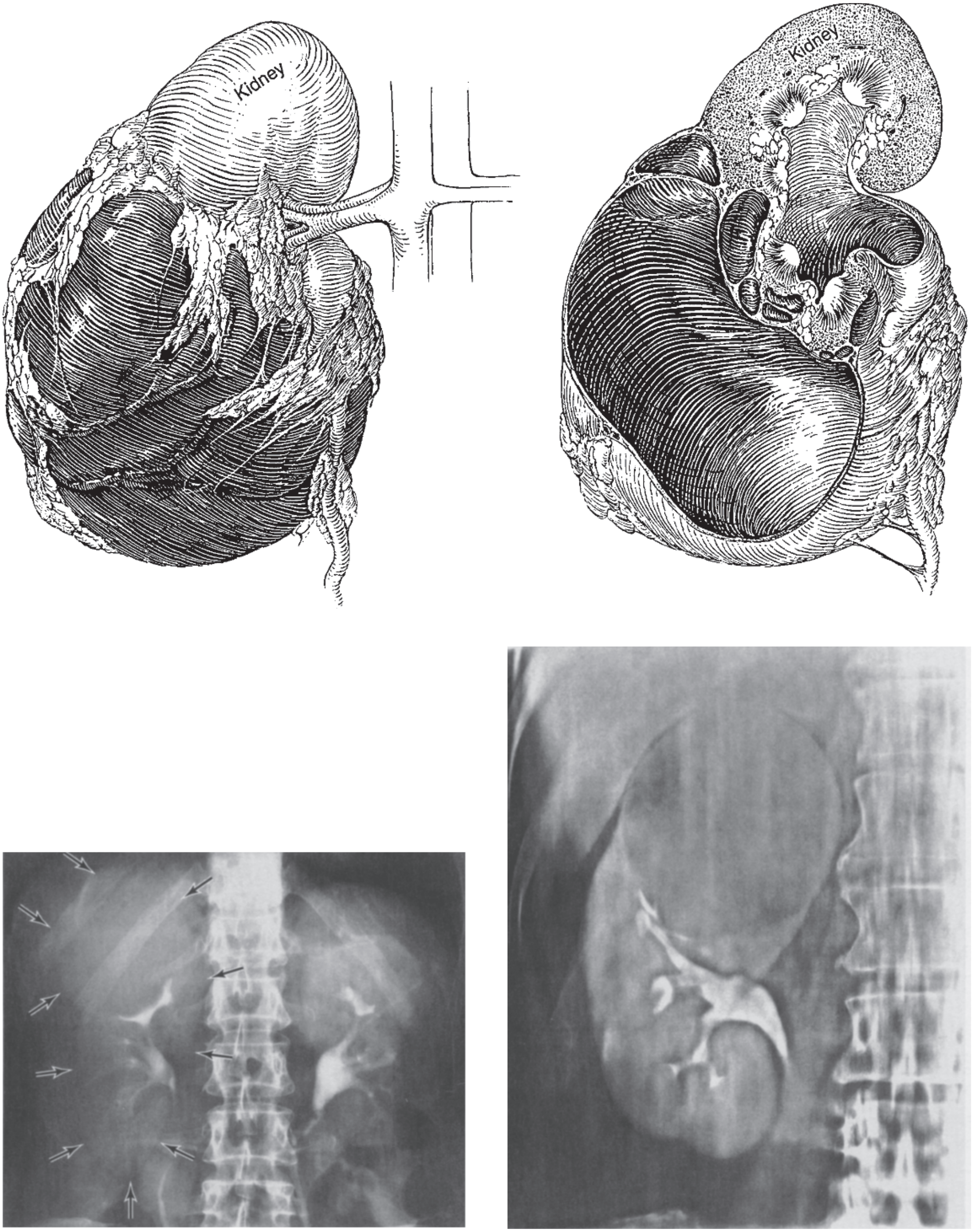
Bilateral hydronephrosis (determined by the presence of congenital or acquired ureteral obstruction) may present bilateral flank masses and signs of impairment of renal function, but ultrasonography shows changes quite different from those of the polycystic kidney.

Bilateral renal tumor is rare but may mimic polycystic kidney disease perfectly on urography. Tumors are usually localized to one portion of the kidney, whereas cysts are quite diffusely distributed. The total renal function should be normal with unilateral tumor but is usually depressed in patients with polycystic kidney disease. CT scan may be needed at times to differentiate between the two conditions.

In **von Hippel–Lindau disease** (angiomatous cerebellar cyst, angiomatosis of the retina, and tumors or cysts of the pancreas), multiple bilateral cysts, or adenocarcinomas of both kidneys may develop. The presence of other stigmas should confirm the diagnosis. CT, angiography, sonography, or scintiphotography should be definitive.

Tuberous sclerosis (convulsive seizures, mental retardation, and adenoma sebaceum) is typified by hamartomatous tumors often involving the skin, brain, retinas, bones, liver, heart, and kidneys (see Chapter 21). The renal lesions are usually multiple and bilateral and are angiomyolipomas microscopically. The presence of other stigmas and use of CT or sonography should make the differentiation.

A **simple cyst** (see section following this one) is usually unilateral and single; total renal function should be normal. Urograms usually show a single lesion (Figure 32–2), whereas polycystic kidney disease is bilateral and has multiple filling defects.



▲ **Figure 32–2.** Simple cyst. ***Upper left:*** Large cyst displacing lower pole laterally. ***Upper right:*** Section of kidney showing one large and a few small cysts. ***Lower left:*** Excretory urogram showing soft-tissue mass in upper pole of right kidney. Elongation and distortion of upper calyces by cyst. ***Lower right:*** Infusion nephrotomogram showing large cyst in upper renal pole distorting upper calyces and dislocating upper portion of kidney laterally.

Complications

For reasons that are not clear, pyelonephritis is a common complication of polycystic kidney disease. It may be asymptomatic; pus cells in the urine may be few or absent. Stained smears or quantitative cultures make the diagnosis. A gallium-67 citrate scan will reveal the sites of infection, including abscess, although CT is the most accurate modality for diagnosis and follow-up of abscesses (Browne et al, 2004).

Infection of cysts is associated with pain and tenderness over the kidney and a febrile response. The differential diagnosis between infection of cysts and pyelonephritis may be difficult, but here again a gallium scan will prove helpful. Positron emission tomography (PET) using 18-fluorodeoxyglucose has also become promising as a means to accurately diagnose and localize suspected infected renal cysts (Calvet, 2015). In rare instances, gross hematuria may be so brisk and persistent as to endanger life.

Treatment

A. General Measures

The patient should be placed on a low-protein diet (0.5–0.75 g/kg/day of protein) and forced to consume fluids at a volume of ≥3000 mL per day. Physical activity may be permitted within reason, but strenuous exercise is contraindicated. When the patient is in a state of absolute renal insufficiency, one should treat the same as for uremia from any cause. Hypertension should be controlled. Hemodialysis may be indicated.

B. Surgery

There is no evidence that excision or decompression of cysts improves renal function. If a large cyst is found to be compressing the upper ureter, causing obstruction and further interfering with renal function, it should be resected or aspirated. When the degree of renal insufficiency becomes life-threatening, chronic dialysis or renal transplantation should be considered.

C. Medical Management

Traditionally, treatment for adult polycystic kidney disease has been conservative and supportive. Vasopressin V2 receptor antagonists such as tolvaptan are being studied as possible medical agents to slow disease progression by reducing kidney cyst cell proliferation. They carry the potential side effect of transaminitis and hepatotoxicity (Barnawi et al, 2018).

D. Treatment of Complications

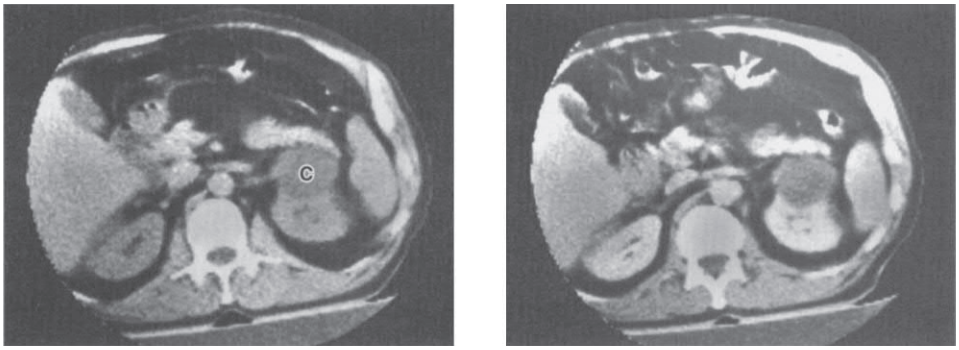
Pyelonephritis must be rigorously treated to prevent further renal damage. Infection of cysts requires surgical drainage. If bleeding from one kidney is so severe that exsanguination is possible, nephrectomy or embolization of the renal or, preferably, the segmental artery must be considered as a lifesaving measure. Concomitant diseases (eg, tumor, obstructing stone) may require definitive surgical treatment.

Prognosis

When the disease affects children, it has a very poor prognosis. The large group presenting clinical signs and symptoms after age 35–40 years has a somewhat more favorable prognosis. Although there is wide variation, these patients seldom live longer than 5 or 10 years after the diagnosis is made, unless dialysis is made available or renal transplantation is done.

SIMPLE (SOLITARY) CYST

Simple cyst (Figures 32–2 and 32–3) of the kidney is usually unilateral and single but may be multiple and multilocular and, more rarely, bilateral. It differs from polycystic kidneys both clinically and pathologically.



▲ **Figure 32–3.** Left renal cyst. ***Left:*** Computed tomography (CT) scan shows a homogeneous low-density mass (C) arising from anterior border of left kidney just posterior to tail of the pancreas. The CT attenuation value was similar to that of water, indicating a simple renal cyst. ***Right:*** After intravenous injection of contrast material, the mass did not increase in attenuation value, adding further confirmatory evidence of its benign cystic nature.

Etiology and Pathogenesis

Whether simple cyst is congenital or acquired is not clear. Its origin may be similar to that of polycystic kidneys; that is, the difference may be merely one of degree. On the other hand, simple cysts have been produced in animals by causing tubular obstruction and local ischemia; this suggests that the lesion can be acquired.

As a simple cyst grows, it compresses and thereby may destroy renal parenchyma, but rarely does it destroy so much renal tissue that renal function is impaired. A solitary cyst may be placed in such a position as to compress the ureter, causing progressive hydronephrosis. Infection may complicate the picture.

Acquired cystic disease of the kidney can arise as an effect of chronic dialysis. The spontaneous regression of cysts has occasionally been noted.

Pathology

Simple cysts usually involve the lower pole of the kidney. Those that produce symptoms average about 10 cm in diameter, but a few are large enough to fill the entire flank. They usually contain a clear amber fluid. Their walls are quite thin, and the cysts are "blue-domed" in appearance. Calcification of the sac is occasionally seen. About 5% contain hemorrhagic fluid, and possibly one-half of these have papillary cancers on their walls.

Simple cysts are usually superficial but may be deeply situated. When a cyst is situated deep inside the kidney, the cyst wall is adjacent to the epithelial lining of the pelvis or calyces, from which it may be separated only with great difficulty. Cysts do not communicate with the renal pelvis (Figure 32–2). Microscopic examination of the cyst wall shows heavy fibrosis and hyalinization; areas of calcification may be seen. The adjacent renal tissue is compressed and fibrosed. Numerous cases of simple cysts have been reported in children. However, large cysts are rare in children; the presence of cancer must therefore be ruled out.

Multilocular renal cysts may be confused with tumor on urography. Sonography usually makes the diagnosis. Occasionally, CT and magnetic resonance imaging (MRI) may be necessary.

The Bosniak classification of simple renal cysts is an aid to determining the chance of malignancy based on imaging criteria. Type I cysts are simple and smooth-walled, with clear fluid; type II cysts are also benign, but may have minimal septations and a small fine rim of calcification; type III cysts are more complex, with more calcification, increasing septations, and a thick cyst wall; type IV cysts have a thickened irregular wall, often with calcifications, and a mass may be noted inside the cyst, suggesting carcinoma. Numerous variations of the findings are used as a guide in the diagnosis of renal cancer. The prevalence of malignancy increases as cyst complexity increases, with pooled malignancy rates of 3.2%, 6%, 6.7%, 55.1%, and 91% for Bosniak type I, II, IIF, III, IV cysts, respectively (Sevcenco et al, 2017).

Clinical Findings

A. Symptoms

Pain in the flank or back, usually intermittent and dull, is not uncommon. If bleeding suddenly distends the cyst wall, pain may come on abruptly and be severe. Gastrointestinal symptoms are occasionally noted and may suggest peptic ulcer or gallbladder disease. The patient may discover a mass in the abdomen, although cysts of this size are unusual. If the cyst becomes infected, the patient usually complains of pain in the flank, malaise, and fever.

B. Signs

Physical examination is usually normal, although occasionally a mass in the region of the kidney may be palpated or percussed. Tenderness in the flank may be noted if the cyst becomes infected.

C. Laboratory Findings

Urinalysis is usually normal. Microscopic hematuria is rare. Renal function tests are normal unless the cysts are multiple and bilateral (rare). Even in the face of extensive destruction of one kidney, compensatory hypertrophy of the other kidney will maintain normal total function.

D. CT Scanning

Computed tomographic scanning appears to be the most accurate means of differentiating between renal cysts and tumors (Figure 32–3). Cysts have an attenuation approximating that of water, whereas the density of tumors is similar to that of normal parenchyma. The density of parenchyma increases with the intravenous injection of radiopaque fluid, but a cyst remains unaffected. The wall of a cyst is sharply demarcated from the renal parenchyma; a tumor is not. The wall of a cyst is thin, while that of a tumor is not. CT scan may well supplant cyst puncture in the differentiation of cyst and tumor in many cases.

E. Renal Ultrasonography

Renal ultrasonography is a noninvasive diagnostic technique that differentiates between a cyst and a solid mass in a high percentage of cases. If findings on ultrasonography are also compatible with a cyst, a needle can be introduced into the cyst under ultrasonographic control and the cyst can be aspirated. To bolster accuracy of ultrasound, contrast enhanced ultrasound (CEUS) has been proposed as a means to detect enhancement of renal cysts and obviate the need for further evaluation with CT or MRI (Gulati et al, 2015).

F. Isotope Scanning

A rectilinear scan clearly delineates the mass but does not differentiate a cyst from a tumor. The technetium scan, which is enabled by the injection of a drug known as **sestamibi**, reveals that the mass is indeed avascular.

G. Percutaneous Cyst Aspiration with Cystography

If the studies listed leave some doubt about the differentiation between cyst and tumor, aspiration may be done (see "Treatment" section, below).

Differential Diagnosis

Carcinoma of the kidney also occupies space but tends to lie more deeply in the organ and therefore causes more distortion of the calyces. Hematuria is common with tumor but rare with cyst. If a solid tumor overlies the psoas muscle, the edge of the muscle is obliterated on the plain film; it can be seen through a cyst, however. Evidence of metastases (ie, loss of weight and strength, palpable supraclavicular nodes, chest film showing metastatic nodules), erythrocytosis, hypercalcemia, and increased sedimentation rate suggest cancer. It must be remembered, however, that the walls of a simple cyst may undergo cancerous degeneration. Sonography, CT scan, or MRI should be almost definitive in differential diagnosis. It is wise to assume that all space-occupying lesions of the kidneys are cancers until proven otherwise.

Polycystic kidney disease is almost always bilateral. Diffuse calyceal and pelvic distortion is the rule. A simple cyst is usually solitary and unilateral. Polycystic kidney disease is usually accompanied by impaired renal function and hypertension; a simple cyst is not.

Renal cortical abscess is rare. A history of skin infection a few weeks before the onset of fever and local pain may be obtained. CT scan of the kidney will usually show signs of the abscess. The kidney may be fixed; this can be demonstrated by comparing the position of the kidney when the patient is supine and upright. Angiography demonstrates an avascular lesion. A gallium-67 scan demonstrates the inflammatory nature of the lesion, but an infected simple cyst might have a similar appearance.

Hydronephrosis may present the same symptoms and signs as simple cyst, but the urograms are quite different. A cyst causes calyceal distortion; with hydronephrosis, dilatation of the calyces and pelvis due to an obstruction is present. Acute or subacute hydronephrosis usually produces more local pain because of increased intrapelvic pressure and is more apt to be complicated by infection.

Extrarenal tumor (eg, adrenal, mixed retroperitoneal sarcoma) may displace a kidney, but rarely does it invade it and distort its calyces. If an echinococcal cyst of the kidney does not communicate with the renal pelvis, it may be difficult to differentiate it from a solitary cyst, for no scoleces or hooklets will be present in the urine. The wall of a hydatid cyst often reveals calcification on x-ray examination (see Figure 14–5). A skin sensitivity test (Casoni) for hydatid disease may prove helpful.

Complications (Rare)

Spontaneous infection in a simple cyst is rare, but when it occurs, it is difficult to differentiate from carbuncle. Hemorrhage into the cyst sometimes occurs. If sudden, it causes severe pain. The bleeding may be caused by a complicating carcinoma arising on the wall of the cyst.

Hydronephrosis may develop if a cyst of the lower pole impinges on the ureter. This by itself may cause pain from back pressure of urine in the renal pelvis. This obstruction may lead to renal infection.

Treatment

A. Specific Measures

1. If renal sonography, CT, or MRI does not lead to a definitive diagnosis, renal angiography or needle aspiration of the cyst may be necessary. Should aspiration be necessary, it can be done under sonographic guidance. The recovery of clear fluid is characteristic of a benign cyst, which should be confirmed by cytologic evaluation. In some centers, contrast radiopaque fluid is injected into the cyst after aspiration for a more thorough evaluation of the cyst wall. A smooth cyst wall, free of irregularities, supports the presence of a benign cyst. If the aspirate contains blood, surgical exploration should be considered, because the chances are great that the growth is cancerous.
2. If the diagnosis can be clearly established, one should consider leaving the cyst alone, since it is rare for a cyst to harm the kidney. Sonography is useful in follow-up of patients with cysts.

B. Treatment of Complications

If the cyst becomes infected, intensive antimicrobial therapy should be instituted; antimicrobial drugs have been found to attain very low concentrations in the cyst fluid. Therefore, percutaneous drainage is often required. Surgical excision of the extrarenal portion of the cyst wall and drainage are curative when percutaneous drainage fails.

If hydronephrosis is present, excision of the obstructing cyst will relieve the ureteral obstruction. Pyelonephritis in the involved kidney should suggest urinary stasis secondary to impaired ureteral drainage. Removal of the cyst and consequent relief of urinary back pressure make antimicrobial therapy more effective.

Prognosis

Simple cysts can be diagnosed with great accuracy using sonography and CT scan. Yearly sonography is recommended as a method of following the cyst for changes in size, configuration, and internal consistency. CT scan may be done if changes suggest carcinoma, and aspiration may then be performed, if necessary, to establish a diagnosis. Most cysts cause little difficulty.

RENAL FUSION

Approximately 1 in 1000 individuals has some type of renal fusion; the most common type is the "horseshoe" kidney. The fused renal mass almost always contains two excretory systems and therefore two ureters. The renal tissue may be divided equally between the two flanks, or the entire mass may be on one side. Even in the latter case, the two ureters open at their proper places in the bladder.

Etiology and Pathogenesis

It appears that this fusion of the two metanephroi occurs early in embryologic life, when the kidneys lie low in the pelvis. For this reason, they seldom ascend to the high position that normal kidneys assume. They may even remain in the true pelvis. Under these circumstances, such a kidney may derive its blood supply from many vessels in the area (eg, aorta, iliacs). Although horseshoe kidneys are commonly described as being held in the pelvis by the inferior mesenteric artery (IMA), the isthmus of the horeshoe kidney is found inferior to the IMA in only 40% of cases (Taghavi et al, 2016). In patients with both ectopia and fusion, 78% have extraurologic anomalies and 65% exhibit other genitourinary defects.

Pathology (Figure 32–4)

Because the renal masses fuse early, normal rotation cannot occur; therefore, each pelvis lies on the anterior surface of its organ. Thus, the ureter must ride over the isthmus of a horseshoe kidney or traverse the anterior surface of the fused kidney. Some degree of ureteral compression may arise from this or from obstruction by one or more aberrant blood vessels. The incidence of hydronephrosis and, therefore, infection is high. Vesicoureteral reflux has frequently been noted in association with fusion.

In horseshoe kidney, the isthmus usually joins the lower poles of each kidney; each renal mass lies lower than normal. The axes of these masses are vertical, whereas the axes of normal kidneys are oblique to the spine, because they lie along the edges of the psoas muscles. On rare occasions, the two nephric masses are fused into one mass containing two pelves and two ureters. The mass may lie in the midline in order to open into the bladder at the proper point (crossed renal ectopy with fusion).

Clinical Findings

A. Symptoms

Most patients with fused kidneys have no symptoms. Some, however, develop ureteral obstruction. Gastrointestinal symptoms (renodigestive reflex) mimicking peptic ulcer, cholelithiasis, or appendicitis may be noted. Infection is apt to occur if ureteral obstruction and hydronephrosis or calculus develops.

B. Signs

Physical examination results are usually negative unless the abnormally placed renal mass can be felt. With horseshoe kidney, it may be possible to palpate a mass over the lower lumbar spine (the isthmus). In the case of crossed ectopy, a mass may be felt in the flank or lower abdomen.

C. Laboratory Findings

Urinalysis is normal unless there is infection. Renal function is normal unless disease coexists in each of the fused renal masses.

D. X-Ray Findings

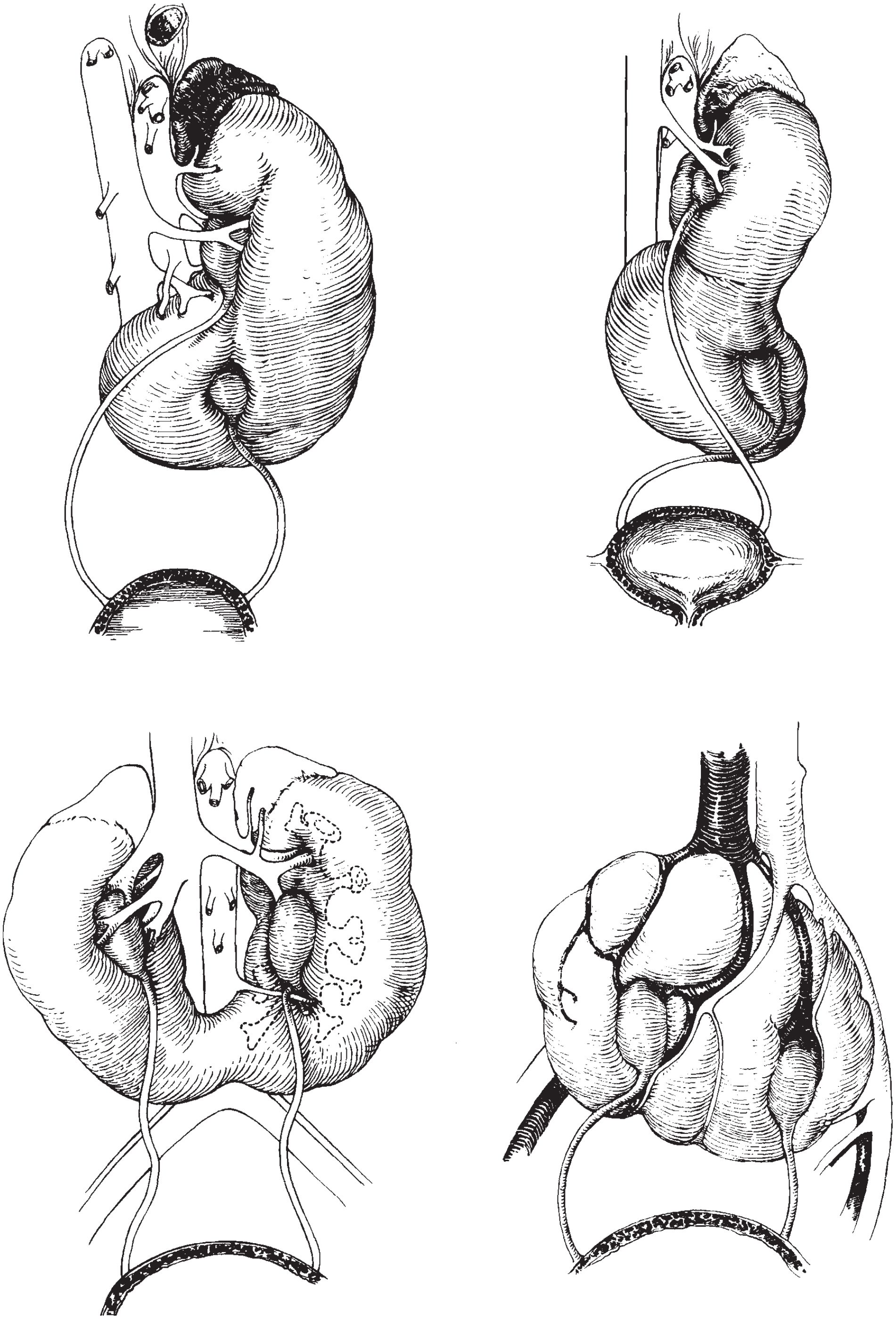
In the case of horseshoe kidney, the axes of the two kidneys, if visible on a plain film, are parallel to the spine. At times, the isthmus can be identified. The plain film may also reveal a large soft-tissue mass in one flank, yet not show a renal shadow on the other side. Excretory urograms establish the diagnosis if the renal parenchyma has been maintained. The increased density of the renal tissue may make the position or configuration of the kidney more distinct. Urograms also visualize the pelvis and ureters.

1. With horseshoe kidney, the renal pelves lie on the anterior surfaces of their kidney masses, whereas the normal kidney has its pelvis lying mesial to it. The most valuable clue to the diagnosis of horseshoe kidney is the presence of calyces in the region of the lower pole that point medially and lie medial to the ureter (Figure 32–4).
2. Crossed renal ectopy with fusion shows two pelves and two ureters. One ureter must cross the midline in order to empty into the bladder at the appropriate point (Figure 32–4).
3. A cake or lump kidney may lie in the pelvis (fused pelvis kidney), but again its ureters and pelves will be shown (Figure 32–4). It may compress the dome of the bladder.

Computed tomographic scan clearly outlines the renal mass but is seldom necessary for diagnosis. With pelvic fused kidney or one lying in the flank, the plain film taken with ureteral catheters in place gives the first hint of the diagnosis. Retrograde urograms show the position of the pelves and demonstrate changes compatible with infection or obstruction. Renal scanning delineates the renal mass and its contour, as does sonography.

Differential Diagnosis

Separate kidneys that fail to undergo normal rotation may be confused with horseshoe kidneys. They lie along the edges of the psoas muscles, whereas the poles of a horseshoe kidney lie parallel to the spine and the lower poles are placed on the psoas muscles. The calyces in the region of the isthmus of a horseshoe kidney point medially and lie close to the spine.



▲ **Figure 32–4.** Renal fusion. ***Upper left:*** Crossed renal ectopy with fusion. The renal mass lies in the left flank. The right ureter must cross over the midline. ***Upper right:*** Example of “sigmoid” kidney. ***Lower left:*** Horseshoe kidney. Pelves are anterior. Note the aberrant artery obstructing the left ureter and the low position of renal mass. ***Lower right:*** Pelvic kidney. Pelves are placed anteriorly. Note the aberrant blood supply.

The diagnosis of fused or lump kidney may be missed on excretory urograms if one of the ureters is markedly obstructed, so that a portion of the kidney, pelvis, and ureter fails to visualize. Infusion urograms or retrograde urograms demonstrate both excretory tracts in the renal mass.

Complications

Fused kidneys are prone to ureteral obstruction because of a high incidence of aberrant renal vessels and the necessity for one or both ureters to arch around or over the renal tissue. Hydronephrosis, stone, and infection, therefore, are common. A large fused kidney occupying the concavity of the sacrum may cause dystocia during pregnancy.

Treatment

No treatment is necessary unless obstruction or infection is present. Drainage of a horseshoe kidney may be improved by dividing its isthmus. If one pole of a horseshoe is severely damaged, it may require surgical resection.

Prognosis

In most cases, the outlook is excellent. If ureteral obstruction and infection occur, renal drainage must be improved by surgical means so that antimicrobial therapy will be effective.

ECTOPIC KIDNEY

Congenital ectopic kidney usually causes no symptoms unless complications such as ureteral obstruction or infection develop.

Simple Ectopy

Simple congenital ectopy usually refers to a low kidney on the proper side that failed to ascend normally. It may lie over the pelvic brim or in the pelvis. Rarely, it may be found in the chest. It takes its blood supply from adjacent vessels, and its ureter is short. It is prone to ureteral obstruction and infection, which may lead to pain or fever. At times, such a kidney may be palpable, leading to an erroneous presumptive diagnosis (eg, cancer of the bowel, appendiceal abscess).

Excretory urograms reveal the true position of the kidney. Hydronephrosis, if present, is evident. There is no redundancy of the ureter, as is the case with nephroptosis or acquired ectopy (eg, displacement by large suprarenal tumor). Obstruction and infection may complicate simple ectopy and should be treated by appropriate means.

CROSSED ECTOPY WITHOUT FUSION

In crossed ectopy without fusion, the kidney lies on the opposite side of the body but is not attached to its normally placed mate. Unless two distinct renal shadows can be seen, it may be difficult to differentiate this condition from crossed ectopy with fusion (Figure 32–4). Sonography, angiography, or CT should make the distinction.

ABNORMAL ROTATION

Normally, when the kidney ascends to the lumbar region, the pelvis lies on its anterior surface. Later, the pelvis comes to lie mesially. Such rotation may fail to occur, although this seldom leads to renal disease. Urography demonstrates the abnormal position.

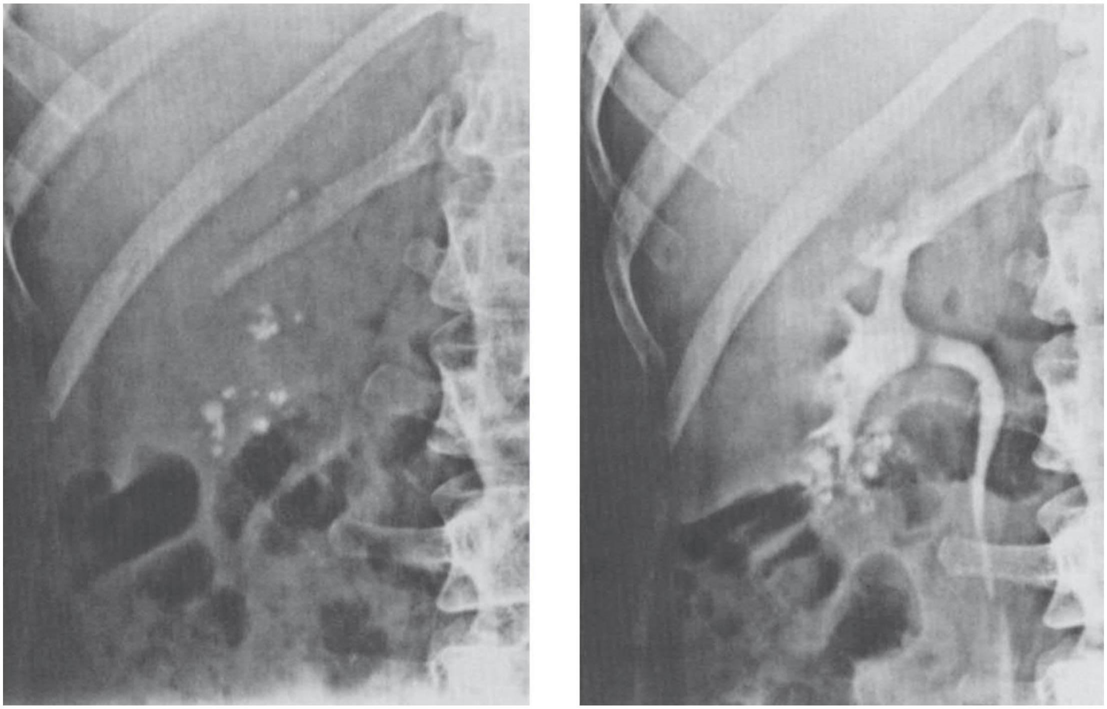
MEDULLARY SPONGE KIDNEY (CYSTIC DILATATION OF THE RENAL COLLECTING TUBULES)

Medullary sponge kidney is a congenital autosomal recessive defect characterized by widening of the distal collecting tubules. It is usually bilateral, affecting all the papillae, but it may be unilateral. At times, only one papilla is involved. Cystic dilatation of the tubules is also often present. Infection and calculi are occasionally seen as a result of urinary stasis in the tubules. It is believed that medullary sponge kidney is related to polycystic kidney disease, but the connection has not been well studied. Its occasional association with hemihypertrophy of the body has been noted in addition to its association with central nervous system (CNS), cardiovascular system, and craniofacial skeleton development congenital abnormalities (Ria et al, 2017).

The only symptoms are those arising from infection and stone formation. The diagnosis is based on results obtained by excretory urograms or contrast-enhanced CT scanning (Figure 32–5). The pelvis and calyces are normal, but dilated (streaked) tubules are seen just lateral to them; many of the dilated tubules contain round masses of radiopaque material (the cystic dilatation). If stones are present, a plain film will reveal small, round calculi in the pyramidal regions just beyond the calyces.

The differential diagnosis includes tuberculosis, healed papillary necrosis, and nephrocalcinosis. Tuberculosis is usually unilateral, and urography shows ulceration of calyces; tubercle bacilli are found on bacteriologic study. Papillary necrosis may be complicated by calcification in the healed stage but may be distinguished by its typical calyceal deformity, the presence of infection, and, usually, impaired renal function. The tubular and parenchymal calcification seen in nephrocalcinosis is more diffuse than that seen with sponge kidney; the symptoms and signs of primary hyperparathyroidism or renal tubular acidosis may be found.

There is no treatment for medullary sponge kidney. Therapy is directed toward managing the complications (eg, pyelonephritis and renal calculi). Only a small percentage of people with sponge kidney develop complications. The overall prognosis is good. A few patients may pass small stones occasionally.



▲ **Figure 32–5.** Medullary sponge kidneys. ***Left:*** Plain film of right kidney showing multiple small stones in its middle portion. ***Right:*** Excretory urogram showing relationship of calculi to calyces. Typically, the calyces are large; the stones are located in the dilated collecting tubules.

ABNORMALITIES OF RENAL VESSELS

A single renal artery is noted in 75–85% of individuals and a single renal vein in an even higher percentage. Aberrant veins and, especially, arteries occur. An aberrant artery passing to the lower pole of the kidney or crossing an infundibulum can cause obstruction and hydronephrosis. These causes of obstruction can be diagnosed on angiography, magnetic resonance imaging, or contrast phase CT.

ACQUIRED LESIONS OF THE KIDNEYS

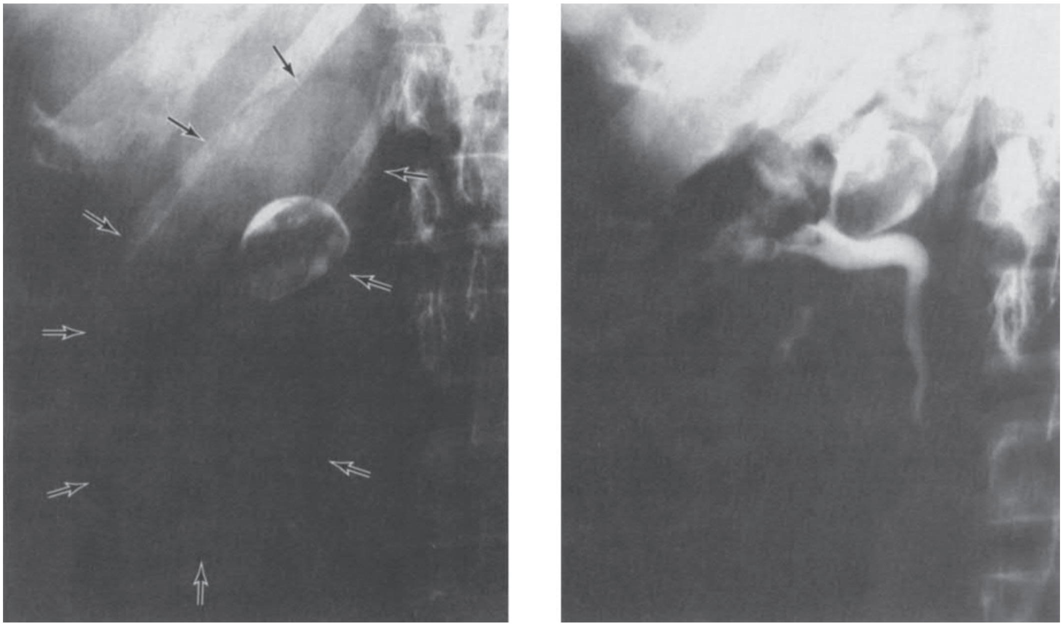
ANEURYSM OF THE RENAL ARTERY

Aneurysm of the renal artery usually results from degenerative arterial disease that weakens the wall of the artery so that intravascular pressure may balloon it out. It is most commonly caused by arteriosclerosis or arterial fibromuscular dysplasia (González et al, 2014), but it may develop secondary to trauma or syphilis. Congenital aneurysms have been reported. Most cases represent an incidental finding on angiography.

Aneurysmal dilatation has no deleterious effect on the kidney unless the mass compresses the renal artery, in which case some renal ischemia and, therefore, atrophy are to be expected. A true aneurysm may rupture, producing a false aneurysm. This is especially likely to occur during pregnancy. The extravasated blood in the retroperitoneal space finally becomes encapsulated by a fibrous covering as organization occurs. An aneurysm may involve a small artery within the renal parenchyma. It may rupture into the renal pelvis or a calyx.

Most aneurysms cause no symptoms unless they rupture, in which case, there may be severe flank pain and even shock. If an aneurysm ruptures into the renal pelvis, marked hematuria occurs. The common cause of death is severe hemorrhage from rupture of the aneurysm. Hypertension is rarely present. A bruit should be sought over the costovertebral angle or over the renal artery anteriorly. If spontaneous or traumatic rupture has occurred, a mass may be palpated in the flank.

A plain film of the abdomen may show an intrarenal or extrarenal ringlike calcification (Figure 32–6). Urograms may be normal or reveal renal atrophy. Some impairment of renal function may be noted if compression or partial obstruction of the renal artery has developed. Aortography delineates the aneurysm. Sonography, MRI, and CT scanning may prove helpful.



▲ **Figure 32–6.** Intrarenal aneurysm of renal artery. ***Left:*** Plain film showing calcified structure over right renal shadow. ***Right:*** Excretory urogram relating calcific mass to pelvis and upper calyx. (Used with permission from CD King.)

The differential diagnosis of rupture of an aneurysm and injury to the kidney is difficult unless a history or evidence of trauma is obtained. A hydronephrotic kidney may present a mass, but renal imaging clarifies the issue.

Because a significant number of noncalcified and large calcified aneurysms rupture spontaneously, the presence of such a lesion is an indication for operation, particularly during pregnancy. The repair of extrarenal aneurysms may be considered, but complications (eg, thrombosis) are not uncommon. If an intrarenal aneurysm is situated in one pole, heminephrectomy may be feasible. If it is in the center of the organ and must be removed, however, nephrectomy is required. Therapeutic occlusion of an aneurysm by intra-arterial injection of autologous muscle tissue has been reported. Thrombin injection can be employed after failure of an endovascular approach (González et al, 2014). Those few patients with hypertension may become normotensive following definitive surgery.

RENAL INFARCTS

Renal infarcts are caused by arterial occlusion. The major causes are subacute infective endocarditis, atrial or ventricular thrombi, arteriosclerosis, polyarteritis nodosa, and trauma. A thrombotic process in the abdominal aorta may gradually extend upward to occlude the renal artery. Renal infarcts may be unilateral or bilateral.

If smaller arteries or arterioles become obstructed, the tissue receiving blood from such a vessel will first become swollen and then undergo necrosis and fibrosis. If the main renal artery becomes occluded, the entire kidney will react in kind. The kidney may become functionless and atrophic, therefore, as it undergoes necrosis and fibrosis.

Partial renal infarction is a silent disease, but it can result in flank pain and microscopic or gross hematuria. Sudden and complete infarction may cause renal or chest pain and at times gross or microscopic hematuria. Proteinuria and leukocytosis are found. **Epitheluria**, representing sloughing of renal tubular cells, has been noted. Tenderness over the flank may be elicited. The kidney is not significantly enlarged by arterial occlusion.

Computed tomographic scan may fail to have contrast enhancement in a portion of the kidney with partial infarction; with complete infarction, none of the radiopaque fluid is excreted. If complete renal infarction is suspected, a radioisotope renogram will show little or no radioactivity. A similar picture is seen on CT scans performed after injection of radiopaque contrast medium. Even though complete loss of measurable function has occurred, renal circulation may be restored spontaneously in rare instances. Renal angiography or CT makes the definitive diagnosis. A dynamic technetium scan will reveal no perfusion of the affected renal vasculature.

During the acute phase, infarction may mimic ureteral stone. With stone, the excretory urogram may also show lack of renal function, but even so, there is usually enough medium in the tubules for a "nephrogram" to be obtained. This will not occur with complete infarction. Evidence of a cardiac or vascular lesion is helpful in arriving at a proper diagnosis.

The complications are related to infarcts arising from the primary cardiovascular disease, including emboli to other organs. In a few cases, hypertension may develop a few days or weeks after the infarction. It may later subside.

Although emergency surgical intervention has been done, it has become clear that anticoagulation therapy is the treatment of choice. It has been shown that urokinase, heparin, warfarin, and antiplatelet agents can be used to treat the embolus (Oh et al, 2016). Renal function returns in most cases.

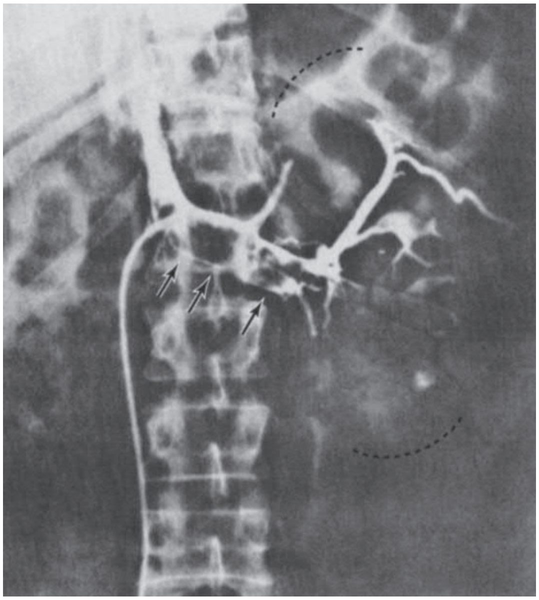
THROMBOSIS OF THE RENAL VEIN

Thrombosis of the renal vein is rare in adults. It is frequently unilateral and usually associated with membranous glomerulonephritis and nephrotic syndrome. Invasion of the renal vein by tumor or retroperitoneal disease can be the cause. Thrombosis of the renal vein may occur as a complication of severe dehydration and hemoconcentration in children with severe diarrhea from ileocolitis. The thrombosis may extend from the vena cava into the peripheral venules or may originate in the peripheral veins and propagate to the main renal vein. The severe passive congestion that develops causes the kidney to swell and become engorged. Degeneration of the nephrons ensues. There is usually flank pain, and hematuria may be noted. A large, tender mass is often felt in the flank. Thrombocytopenia may be noted. The urine contains albumin and red cells. In the acute stage, urograms show poor or absent secretion of the radiopaque material in a large kidney. Stretching and thinning of the calyceal infundibula may be noted. Clots in the pelvis may cause filling defects. Later, the kidney may undergo atrophy.

Ultrasonography shows the thrombus in the vena cava in 50% of cases. The involved organ is enlarged. CT scan is also a valuable diagnostic tool; visualization of the thrombus can be noted in a high percentage of cases. MRI has proved to be a very sensitive diagnostic tool. Renal angiography reveals stretching and bowing of small arterioles. In the nephrographic phase, the pyramids may become quite dense. Late films may show venous collaterals. Venacavography or, preferably, selective renal venography demonstrates the thrombus in the renal vein (Figure 32–7) and, at times, in the vena cava.

The symptoms and signs resemble obstruction from a ureteral calculus. The presence of a stone in the ureter should be obvious; some degree of dilatation of the ureter and pelvis also should be expected. Clot obstruction in the ureter must be differentiated from an obstructing calculus.

While thrombectomy and even nephrectomy have been recommended in the past, it has become increasingly clear that medical treatment is usually efficacious. The use of heparin anticoagulation in the acute phase and warfarin chronically offers satisfactory resolution of the problems in most patients. In infants and children, it is essential to correct fluid and electrolyte problems and administer anticoagulants. Fibrinolytic therapy has also been successful. Renal function is usually fully recovered.



▲ **Figure 32–7.** Thrombosis of renal vein. Selective left renal venogram showing almost complete occlusion of vein. Veins to lower pole failed to fill. Note the large size of kidney.

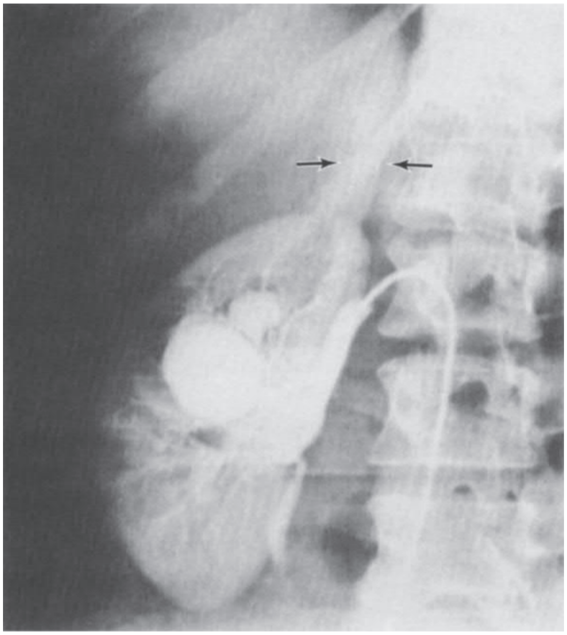
ARTERIOVENOUS FISTULA

Arteriovenous fistula may be congenital (25%) or acquired. A number of these fistulas have been reported following needle biopsy of the kidney or trauma to the kidney. A few have occurred following nephrectomy secondary to suture or ligature occlusion of the pedicle. These require surgical repair. A few have been recognized in association with adenocarcinoma of the kidney. They can also occur as a complication of partial nephrectomy (Linte et al, 2017).

A thrill can often be palpated and a murmur heard both anteriorly and posteriorly. In cases with a wide communication, the systolic blood pressure is elevated, and a widened pulse pressure is noted. Renal angiography or isotopic scan establishes the diagnosis. CT scan, sonography, and, more recently, duplex ultrasound with color flow, are particularly helpful. Arteriovenous fistula involving the renal artery and vein requires surgical repair or nephrectomy. Most, however, can be occluded by embolization, balloon, or steel coil. Those that develop secondary to renal biopsy tend to heal spontaneously.

ARTERIOVENOUS ANEURYSM

About 100 instances of this lesion have been reported (Figure 32–8). Most follow trauma. Hypertension is to be expected and is associated with high-output cardiac



▲ **Figure 32–8.** Arteriovenous aneurysm. Selective renal angiogram. Note the aneurysm in center of kidney, with prompt filling of the vena cava (shown by *arrows*).

failure. A bruit is usually present. Nephrectomy is usually indicated.

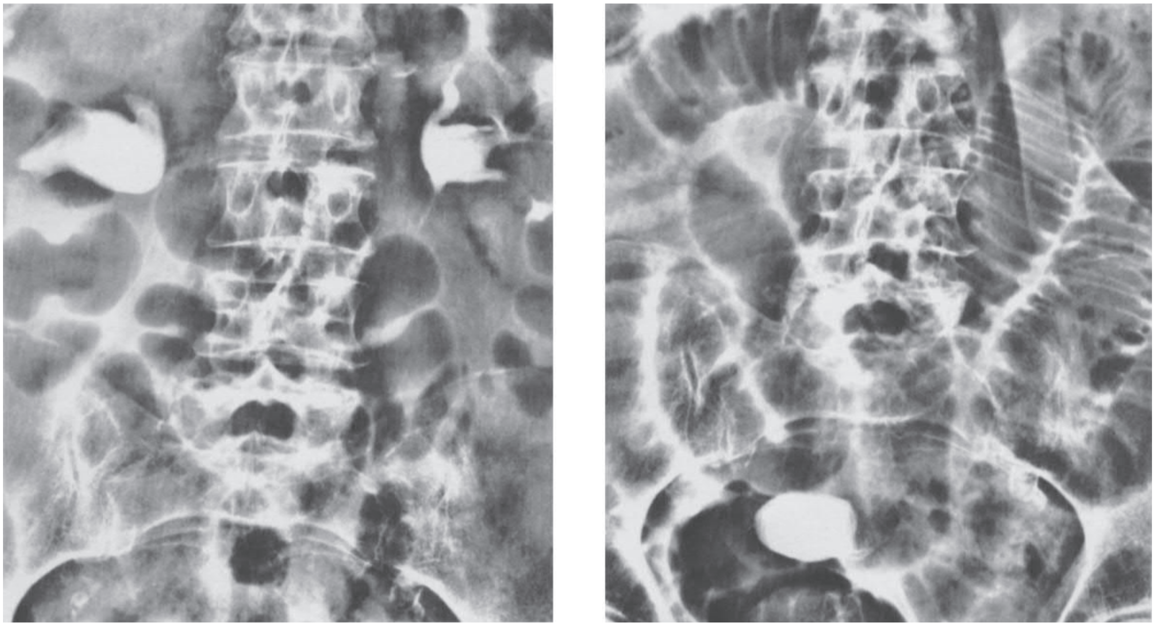
RENOALIMENTARY FISTULA

Over 150 instances of renoalimentary fistula have been reported (Lin et al, 2018). They usually involve the stomach, duodenum, or adjacent colon, although fistula formation with the esophagus, small bowel, appendix, and rectum has been reported.

The underlying cause is usually a pyonephrotic kidney or renal cell carcinoma that becomes adherent to a portion of the alimentary tract and then ruptures spontaneously, thus creating a fistula (Figure 32–9). A few cases following trauma have been reported. The patient is apt to have symptoms and signs of acute pyelonephritis. Urography may show radiopaque material escaping into the gastrointestinal tract. Gastrointestinal series may also reveal the connection with the kidney. The treatment is nephrectomy with closure of the opening into the gut.

RENOBRONCHIAL FISTULA

Renobronchial fistulas are rare. They are caused by rupture of an infected, calculus kidney through the diaphragm.



▲ **Figure 32–9.** Nephroduodenal fistula and small-bowel obstruction from renal staghorn calculus. ***Left:*** Excretory urogram showing nonfunction of right kidney; staghorn stone. ***Right:*** Patient presented with symptoms and signs of bowel obstruction 4 years later. Plain film showing dilated loops of small bowel down to a point just proximal to ileocecal valve. Obstruction due to stone extruded into duodenum. (Used with permission from CD King.)

BIBLIOGRAPHY

Congenital Anomalies of the Kidneys

General

Calisti A et al: The risk of associated urological abnormalities in children with pre and postnatal occasional diagnosis of solitary, small or ectopic kidney: Is a complete urological screening always necessary? World J Urol 2008;26(3):281–284.

Donohue RE, Fauver HE: Unilateral absence of the vas deferens: A useful clinical sign. JAMA 1989;261:1180.

Hálek J et al: Diagnostic accuracy of postnatal ultrasound screening for urinary tract abnormalities. Pediatr Nephrol 2010;25(2): 281–287.

Sheih CP et al: Renal abnormalities in schoolchildren. Pediatrics 1989;84:1086.

Yoshida J et al: Mass screening for early detection of congenital kidney and urinary tract abnormalities in infancy. Pediatr Int 2003;45:142.

Agenesis

Bienstock JL, Birsner ML, Coleman F, Hueppchen NA: Successful in utero intervention for bilateral renal agenesis. Obstet Gynecol 2014;124:413–415.

Kaneyama K et al: Associated urologic anomalies in children with solitary kidney. J Pediatr Surg 2004;39:85.

Laurichesse Delmas H, et al: Congenital unilateral renal agenesis: Prevalence, prenatal diagnosis, associated anomalies. Data from two birth-defect registries. Birth Defects Res 2017;109: 1204–1211.

Ouden van den D et al: Diagnosis and management of seminal vesicle cysts associated with ipsilateral renal agenesis: A pooled analysis of 52 cases. Eur Urol 1998;33:433.

Spira EM et al: Sonographic long-term study: Paediatric growth charts for single kidneys. Arch Dis Child 2009;94(9): 693–698.

Thomas AN, McCullouh LB: Evidence-based, ethically justified counseling for fetal bilateral renal agenesis. J Perinat Med 2017; 45:585–594.

Hypoplasia

Saborio P, Scheinman J: Genetic renal disease. Curr Opin Pediatr 1998;10:174.

Supernumerary Kidneys

Keskin S, Batur A, Keskin Z, Koc A, Ozcan IF: Bilateral supernumerary kidney: A very rare presentation. Iran J Radiol 2014;11: 10–12.

Dysplasia and Multicystic Kidney

Alconcher L, Tombesi M: Multicystic dysplastic kidney detected by prenatal ultrasonography: Conservative management. Pediatr Nephrol 2005;20:1024.

Eickmeyer AB, et al: The natural history of the multicystic dysplastic kidney—Is limited follow-up warranted? J Pediatr Urol 2014;10:655–661.

Mattioli G et al: Nephrectomy for multicystic dysplastic kidney and renal hypodysplasia in children: Where do we stand? Pediatr Surg Int 2010;26(5):523–528.

McMann LP et al: Magnetic resonance urography in the evaluation of prenatally diagnosed hydronephrosis and renal dysgenesis. J Urol 2006;176(4 Pt 2):1786–1792.

Shaheen IS et al: Multicystic dysplastic kidney and pelviureteric junction obstruction. Pediatr Surg Int 2005;21:282.

Singh S et al: Clinico-pathological profile of 22 cases of cystic renal dysplasia. Indian J Pathol Microbiol 2007;50(1):6–10.

Welch TR, Wacksman J: The changing approach to multicystic dysplastic kidney in children. J Pediatr 2005;146:723.

Adult Polycystic Kidney Disease

Avni FE, Hall M: Renal cystic diseases in children: New concepts. Pediatr Radiol 2010;40(6):939–946.

Barnawi RA, Attar RZ, Alfaer SS, Safdar OY: Is the light at the end of the tunnel nigh? A review of ADPKD focusing on the burden of disease and tolvaptan as a new treatment. Int J Nephrol Renovasc Dis 2018;11:53–67.

Browne RFJ, Zwirewich C, Torreggiani WC: Imaging of urinary tract infection in the adult. Eur Radiol 2004;14(Suppl 3): E168–E183.

Calvet JP: The role of calcium and cyclic *AMP* in PKD. In: Polycystic Kidney Disease. National Institutes of Health, Bethesda, MD, 2015, Chapter 8.

Dambreville S et al; Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP): Renal arterial blood flow measurement by breath-held MRI: Accuracy in phantom scans and reproducibility in healthy subjects. Magn Reson Med 2010;63(4):940–950.

Deacu M et al: Urothelial carcinoma of the renal pelvis associated with cystic disease of the kidney. Rom J Morphol Embryol 2011;52 (1 Suppl):497–501.

Dunn MD et al: Laparoscopic cyst marsupialization in patients with autosomal dominant polycystic kidney disease. J Urol 2001;165:1888.

Ekser B, Rigotti P: Images in clinical medicine. Autosomal dominant polycystic kidney disease. New Engl J Med 2010;363(1):71.

Gulati M, King KG, Gill IS, Pham V, Grant E, Duddalwar VA: Contrast-enhanced ultrasound (CEUS) of cystic and solid renal lesions: A review. Abdom Imaging 2015;40:1982–1996.

Lentine KL et al: Renal function and healthcare costs in patients with polycystic kidney disease. Clin J Am Soc Nephrol 2010; 5(8):1471–1479.

Meijer E et al: Early renal abnormalities in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 2010;5(6): 1091–1098.

Punia RP et al: Unilateral and segmental cystic disease of the kidney. Int J Urol 2005;12:308.

Serra AL et al: Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. New Engl J Med 2010;363(9): 820–829.

Sevcenco S, et al: Malignancy rates and diagnostic performance of the Bosniak classification for the diagnosis of cystic renal lesions in computed tomography—a systematic review and meta-analysis. Eur Radiol 2017;27:2239–2247.

Taskinen S et al: Segmental cystic kidney tumours in children. Scand J Urol Nephrol 2009;43(6):476–481.

Renal Fusion

Taghavi K, Kirkpatrick J, Mirjalili SA: The horseshoe kidney: Surgical anatomy and embryology J Pediatr Urol 2016;12:275–280.

Medullary Sponge Kidney

Ria P, Fabris A, Dalla A, Gianluigi G, Lupo A, Gambaro G: New non-renal congenital disorders associated with medullary sponge kidney (MSK) support the pathogenic role of GDNF and point to the diagnosis of MSK in recurrent stone formers. Urolithiasis 2017;45:359–362.

Simple (Solitary) Cyst

Israel GM et al: Evaluation of cystic renal masses: Comparison of CT and MR imaging by using the Bosniak classification system. Radiology 2004;231:365.

Israel GM, Bosniak MA: An update of the Bosniak renal cyst classification system. Urology 2005;66:484.

Patel NS et al: The characterization of small hypoattenuating renal masses on contrast-enhanced CT. Clin Imaging 2009;33(4):295–300.

Ryu DS, Oh TH: Laparoscopic decortication of large renal cysts: A comparison between the transperitoneal and retroperitoneal approaches. J Laparoendosc Adv Surg Tech A 2009;19(5):629–632.

Terada N et al: The 10-year natural history of simple renal cysts. Urology 2008;71(1):7–11; discussion 11–12.

Warren KS, McFarlane J: The Bosniak classification of renal cystic masses. BJU Int 2005;95:939.

White WM et al: Single-port urological surgery: Single-center experience with the first 100 cases. Urology 2009;74(4):801–804.

Acquired Lesions of the Kidneys

General

Nanda S et al: Inferior vena cava anomalies—A common cause of DVT and PE commonly not diagnosed. Am J Med Sci 2008; 335(5):409–410.

Rawashdeh YF et al: The intrarenal resistive index as a pathophysiological marker of obstructive uropathy. J Urol 2001;165:1397.

Zhang JQ et al: Etiology of spontaneous perirenal hemorrhage: A meta-analysis. J Urol 2002;167:1593.

Infection-Related Renal Disorders

Best CD et al: Clinical and radiological findings in patients with gas-forming renal abscess treated conservatively. J Urol 1999;162:1273.

Cheng CH et al: Renal abscess in children: A 10-year clinical and radiologic experience in a tertiary medical center. Pediatr Infect Dis J 2008;27(11):1025–1027.

Cheng CH et al: Clinical courses of children with acute lobar nephronia correlated with computed tomographic patterns. Pediatr Infect Dis J 2009;28(4):300–303.

Demertzis J, Menias CO: State of the art: Imaging of renal infections. Emerg Radiol 2007;14(1):13–22.

Guzzo TJ et al: Xanthogranulomatous pyelonephritis: Presentation and management in the era of laparoscopy. BJU Int 2009; 104(9):1265–1268.

Hussein N et al: Xanthogranulomatous pyelonephritis in pediatric patients: Effect of surgical approach. Urology 2009;73(6):1247–1250.

Lee BE et al: Recent clinical overview of renal and perirenal abscesses in 56 consecutive cases. Korean J Intern Med 2008;23(3): 140–148.

Li L, Parwani AV: Xanthogranulomatous pyelonephritis. Arch Pathol Lab Med 2011;135(5):671–674.

Loffroy R et al: Xanthogranulomatous pyelonephritis in adults: Clinical and radiological findings in diffuse and focal forms. Clin Radiol 2007;62(9):884–890.

Meng MV et al: Current treatment and outcomes of perinephric abscesses. J Urol 2002;168:1337.

Rogers C et al: Robotic nephrectomy for the treatment of benign and malignant disease. BJU Int 2008;102(11):1660–1665.

Vourganti S et al: Ultrasonographic evaluation of renal infections. Radiol Clin North Am 2006;44(6):763–775.

Aneurysm of the Renal Artery

Cura M et al: Renal aneurysms and pseudoaneurysms. Clin Imaging 2011;35(1):29–41.

González J, Esteban M, Andrés G, Linares E, Martínez-Salamanca JI: Renal artery aneurysms. Curr Urol Rep 2014;15.

Helck A et al: Diagnosis, therapy monitoring and follow up of renal artery pseudoaneurysm with contrast-enhanced ultrasound in three cases. Clin Hemorheol Microcirc 2010;46(2–3):127–137.

Ikeda O et al: Endovascular management of visceral artery pseudoaneurysms: Transcatheter coil embolization using the isolation technique. Cardiovasc Intervent Radiol 2010;33(6): 1128–1134.

Keddis MT et al: Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: Clinical and histopathological correlates. Nephrol Dial Transplant 2010;25(11):3615–3622.

Robinson WP III et al: Favorable outcomes with in situ techniques for surgical repair of complex renal artery aneurysms. J Vasc Surg 2011;53(3):684–691.

Renal Infarcts

Oh YK, et al: Clinical characteristics and outcomes of renal infarction. Am J Kidney Dis 2016;67:243–250.

Thrombosis of the Renal Vein

Akin O et al: Bland and tumor thrombi in abdominal malignancies: Magnetic resonance imaging assessment in a large oncologic patient population. Abdom Imaging 2011;36(1):62–68.

Al-Said J, Kamel O: Changes in renal cortical and medullary perfusion in a patient with renal vein thrombosis. Saudi J Kidney Dis Transpl 2010;21(1):123–127.

Cai S et al: Evaluation of acute renal artery thrombosis or embolism with color Doppler sonography. Clin Imaging 2008;32(5): 367–371.

Ciancio G et al: Long-term survival in patients undergoing radical nephrectomy and inferior vena cava thrombectomy: Single-center experience. Eur Urol 2010;57(4):667–672.

Decoster T et al: Renal colic as the first symptom of acute renal vein thrombosis, resulting in the diagnosis of nephrotic syndrome. Eur J Emerg Med 2009;16(4):170–171.

Demirel N et al: Neonatal thrombo-embolism: Risk factors, clinical features and outcome. Ann Trop Paediatr 2009;29(4):271–279.

Douma RA et al: Incidental venous thromboembolism in cancer patients: Prevalence and consequence. Thromb Res 2010;125(6):e306–e309.

Mehta S, Vijayakumar M: Spontaneous renal vein thrombosis with anti-thrombin III deficiency. Indian J Pediatr 2009;76(9):964–965.

Mahmoodi BK et al; Prevention of Renal and Vascular End-stage Disease (PREVEND) Study Group: Microalbuminuria and risk of venous thromboembolism. JAMA 2009;301(17):1790–1797.

Wahlgren CM et al: Endovascular treatment in postthrombotic syndrome. Vasc Endovascular Surg 2010;44(5):356–360.

Arteriovenous Fistula

Linte CA, Camp JJ, Rettmann ME, Iii DRH, Richard A: Partial vs radical nephrectomy for t1–t2 renal masses in the elderly: Comparison of complications, renal function, and oncologic outcomes. Urologiy 2017;100:151–157.

Renoalimentary Fistula

Lin W, Watts K, Aboumohamed A: Renoalimentary fistula: Case report of a renoduodenal fistula and systematic literature review. Urol Case Reps 2018;18:41–43.

This page intentionally left blank

Diagnosis of Medical Renal Diseases

33

Brian K. Lee, MD; & Flavio G. Vincenti, MD

MEDICAL RENAL DISEASE—OVERVIEW

Medical renal diseases are those that involve principally the parenchyma of the kidneys. Hematuria, proteinuria, pyuria, oliguria, polyuria, pain, renal insufficiency with azotemia, acidosis, anemia, electrolyte abnormalities, and hypertension may occur in a wide variety of disorders affecting any portion of the parenchyma of the kidney, the blood vessels, or the excretory tract.

A complete medical history and physical examination, a thorough examination of the urine, and blood and urine chemistry examinations as indicated are essential initial steps in the workup of any patient.

History and Examination

A. Family History

The family history may reveal disease of genetic origin, for example, tubular metabolic anomalies, polycystic kidneys, unusual types of nephritis, or vascular or coagulation defects that may be essential clues to the diagnosis. First-degree relatives of patients with diabetic renal disease have an enhanced risk of end-stage renal disease, inherited independently of diabetes mellitus. Another area of interest is the association of the nephrin (NPHS1) and podocin (NPHS2) genes in familial forms of focal segmental glomerulosclerosis (FSGS) and the newly recognized clinical significance of apolipoprotein L1 (APOL1) risk variants on the progression of chronic kidney disease (CKD) among African-American patients.

B. Past History

The past personal history should cover infections, injuries, and exposure to toxic agents, anticoagulants, or drugs that may produce toxic or sensitivity reactions. A history of diabetes, hypertensive disease, or autoimmune disease may be obtained. A history of illicit drug use may be relevant, given the recognition that contaminated sources of cocaine can induce antineutrophilic cytoplasmic antibody (ANCA) associated renal disease. The inquiry may also elicit symptoms of uremia, debilitation, and the vascular complications of chronic renal disease, but often, the patient is asymptomatic, and the diagnosis of renal disease is made incidentally on abnormal laboratory findings.

Physical Examination

Pallor, edema, hypertension, retinopathy (either hypertensive or diabetic changes), or stigmata of congenital and hereditary disease may be detected.

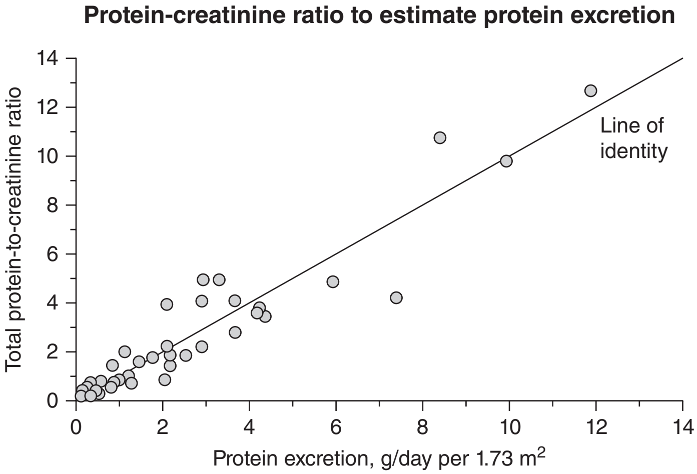
Laboratory Findings

A. Urinalysis

Examination of the urine is the essential part of any investigation of renal disease.

1. Proteinuria—Proteinuria of any significant degree (2–4+) is suggestive of medical renal disease (parenchymal involvement). Formed elements present in the urine additionally establish the diagnosis. Significant proteinuria occurs in immune-mediated glomerular diseases or disorders with glomerular involvement such as diabetes mellitus, myeloma, or amyloidosis. Interstitial nephritis, polycystic kidneys, and other tubular disorders seldom are associated with significant proteinuria. To better quantify the degree of proteinuria, one could either collect a 24-hour urine sample or use a spot urine protein: creatinine ratio (measured in milligrams of protein/mg creatinine) as a surrogate (see Figure 33–1).

2. Erythrocyte casts—Red blood cell casts point to glomerulonephritis. If red blood cell (erythrocyte) casts are not present, microscopic hematuria may or may not be of glomerular origin. Phase contrast microscope study may reveal dysmorphic changes in the erythrocytes (acanthocytes—Mickey Mouse ears) that may be present in the urine in patients with



▲ **Figure 33–1.** This graph illustrates the relation between total 24-hour urinary protein excretion and the total protein-to-creatinine ratio (mg/mg) determined on a random urine specimen. Although there appears to be a close correlation, there can be wide variability in 24-hour protein excretion at a given total protein-to-creatinine ratio. At a ratio of 2, for example, 24-hour protein excretion varied from 2 to almost 8 g/day. (Data from Ginsberg JM, Chang BS, Matarese RA, et al: Use of single voided urine samples to estimate quantitative proteinuria, N Engl J Med. 1983 Dec 22;309(25):1543–1546.)

glomerular disorders (a finding with a sensitivity of 52%, and a specificity of 98%).

3. Fatty casts and oval fat bodies—Tubular cells showing fatty changes occur in degenerative diseases of the kidney (nephrosis, glomerulonephritis, autoimmune disease, amyloidosis, and damage due to toxins such as lead or mercury).

4. Granular casts—These types of casts result from degeneration of cellular casts. They are nondiagnostic of a specific renal disorder but do reflect an inflammatory condition in the kidneys.

B. Other Findings

Abnormal urinary chemical constituents may be the only indication of a metabolic disorder involving the kidneys. These disorders include diabetes mellitus, renal glycosuria, aminoacidurias (including cystinuria), oxaluria, gout, hyperparathyroidism, hemoglobinuria, and myoglobinuria.

Examination of the Kidneys and Urinary Tract

Roentgenographic, sonographic, and radioisotopic studies provide information about the size, structure, blood supply, and function of the kidneys. The advent of computed tomography and magnetic resonance imaging further enhances our ability to visualize the urinary tract and has become indispensable in the diagnosis and management of urologic conditions such as nephrolithiasis and renal tumors. In addition, the high-resolution imaging of vascular and ureteric structures has allowed advances in transplantation, especially in preoperative planning for living kidney donors.

Renal Biopsy

Renal biopsy is a valuable diagnostic procedure. The technique has become well established, providing sufficient tissue for light and electron microscopy and for immunofluorescence examination. Relative contraindications for percutaneous kidney biopsy may include the patients with a congenitally solitary kidney, severe malfunction of one kidney even though function is adequate in the other, bleeding diathesis, and an uncooperative patient. Poorly controlled blood pressure (systolically >160 or diastolically >100 mm Hg) should be controlled prior to performing an invasive procedure such as renal biopsy.

Clinical indications for renal biopsy, in addition to the necessity for establishing a diagnosis, include the need to determine prognosis, to follow progression of a lesion and response to treatment, to confirm the presence of a generalized disease (autoimmune disorder, amyloidosis, sarcoidosis), and to diagnose renal dysfunction in a transplanted kidney. Ultrasound or CT guidance provides a more effective biopsy result. More recently, a laparoscopic approach (with or without robotic assistance) has been used by some urologists. Open renal biopsies have largely been phased out (except under conditions where a patient will concomitantly be undergoing an unrelated urologic procedure).

With the increasing demand for renal biopsies in patients with a bleeding diathesis, especially in those with concomitant liver dysfunction, a transjugular approach has been advocated. However, the success of this procedure is highly dependent on the experience of the center and operators, and diagnostic yield on samples obtained range from 73% to 97%. There have been recent developments in using serum/urinary biomarkers in the diagnosis of kidney dysfunction, and hopefully someday replacing/supplementing the invasive biopsy procedure.

GLOMERULONEPHRITIS

The clinical manifestations of glomerular renal disease are apt to consist only of varying degrees of hematuria, excretion of characteristic formed elements in the urine, proteinuria, and renal insufficiency and its complications. Excluding diabetes, purported immunologic renal diseases are the most common cause of proteinuria and the nephrotic syndrome.

Alterations in glomerular architecture as observed in tissue examined by light microscopy alone can be minimal, nonspecific, and difficult to interpret. For these reasons, specific diagnoses of renal disease require targeted immune fluorescent techniques for demonstrating a variety of antigens, antibodies, and complement fractions. Electron microscopy has complemented these immunologic methods. Tissue analysis can be assisted by blood tests of immunoglobulins (Ig), complement, and other mediators of inflammation.

There are two important humoral mechanisms leading to deposition of antibodies within the glomerulus. These are based on the location of the antigen, whether fixed within the kidney or present in soluble form in circulation. The fixed antigens are either a natural structural element of the glomerulus or foreign materials that have been trapped within the glomerulus for a variety of immunologic or physiochemical reasons. The best examples of the fixed natural antigens are those associated with the glomerular basement membrane (GBM). These antigens are evenly distributed in the GBM and cause characteristic linear IgG deposition, as determined in immunofluorescence studies. This process represents 5% of cases of immune-mediated glomerular disease and is referred to as **anti-GBM disease**. When this is coupled with pulmonary symptoms (antibodies directed against the alveolar membrane), it is known as **Goodpasture's syndrome**. However, most patients with glomerular immune deposits have discontinuous immune aggregates caused by antibody binding to native renal cell antigens or to antigens trapped within the glomerulus. In addition, immune complexes formed in the circulation can deposit and accumulate in the GBM and the mesangium.

A group of immune-mediated nephritides characterized by necrotizing and crescentic architecture and rapid progression are referred to as **pauci-immune glomerular nephritides** because, while antibodies may contribute to the pathogenesis of the disease, they are rarely demonstrated within the glomeruli. These are known as **antineutrophil cytoplasmic antibody (ANCA)** diseases. Circulating antibodies against myeloperoxidase (MPO, P-ANCA) and proteinase 3 (PR3, C-ANCA) have been noted in microscopic angiitis and granulomatosis with polyangiitis (GPA, formerly known as **Wegener's granulomatosis**), respectively.

Cellular immune processes are likely to be stimulated and contribute in different ways in various other forms of glomerulonephritides.

LIKELY IMMUNOLOGIC MECHANISMS

The following classification of glomerulonephritis is based on the mechanism, the presence, and the localization of immune aggregates in the glomeruli.

A. Subepithelial Immune Deposits

1. Postinfectious glomerulonephritis such as poststreptococcal glomerulonephritis.
2. Membranous nephropathy idiopathic or secondary to other causes such as systemic lupus erythematosus, cancer, gold, penicillamine.

B. Subendothelial Immune Deposits

Glomerulonephritis associated with systemic lupus erythematosus, type I idiopathic membranoproliferative glomerulonephritis (MPGN), glomerulonephritis associated with hepatitis C infection, bacterial endocarditis, and shunt nephritis.

C. Mesangial Immune Deposits

IgA nephropathy, Schönlein–Henoch purpura.

D. Anti-GBM Disease

Diffuse linear deposition of Ig.

Immunologic Mechanisms Not Clearly Established

1. Minimal change nephropathy
2. Focal, segmental glomerulosclerosis
3. Hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura
4. ANCA-associated disease: Wegener's granulomatosis and small-vessel vasculitis
5. Type II MPGN (dense deposit disease)
6. C3 glomerulopathy
7. IgG4-related kidney disease

Poststreptococcal Glomerulonephritis

A. Essentials of Diagnosis

- History of streptococcal infection (usual sites include nasopharynx and skin)
- Mild generalized edema, mild hypertension, retinal hemorrhages
- Gross hematuria; protein, erythrocyte casts, granular and hyaline casts, white blood cells (leukocyturia), and renal epithelial cells in urine
- Elevated antistreptolysin O titer, hypocomplementemia

B. General Considerations

Poststreptococcal glomerulonephritis is a disease affecting both kidneys. In most cases, recovery from the acute stage is complete, but progressive involvement may destroy renal tissue, leading to renal insufficiency. Acute glomerulonephritis is most common in children aged 3–10 years. By far the most common cause is an antecedent infection of the pharynx and tonsils or of the skin with group A β-hemolytic streptococci, certain strains of which are nephritogenic. Nephritis occurs in 10–15% of children and young adults who have clinically evident infection with a nephritogenic strain. In children younger than 6 years, pyoderma (impetigo) is the most common antecedent; in older children and young adults, pharyngitis is a common antecedent. Occasionally, nephritis may follow infection due to other agents, hence the more general term **postinfectious glomerulonephritis**.

The pathogenesis of the glomerular lesion has been further elucidated by using new immunologic techniques (immunofluorescence) and electron microscopy. A likely sequel to infection is injury to the mesangial cells in the intercapillary space. The glomerulus may then become more easily damaged by antigen–antibody complexes developing from the immune response to the infection. Complement is deposited in association with IgG or alone in a granular pattern on the epithelial side of the basement membrane.

Gross examination of the involved kidney shows only punctate hemorrhages throughout the cortex. Microscopically, the primary alteration is in the glomeruli, which show proliferation and swelling of the mesangial and endothelial cells of the capillary tuft. The proliferation of capsular epithelium occurs, and around the tuft, there are collections of leukocytes, erythrocytes, and exudate. Edema of the interstitial tissue and cloudy swelling of the tubular epithelium are common. When severe, typical histologic findings in glomerulitis are enlarging crescents that become hyalinized and converted into scar tissue and obstruct the circulation through the glomerulus. Degenerative changes occur in the tubules, with fatty degeneration, necrosis, and ultimately scarring of the nephron.

C. Clinical Findings

1. Symptoms and signs—Often the disease is mild, and there may be no reason to suspect renal involvement unless the urine is examined. In severe cases, about 2 weeks after the acute streptococcal infection, the patient has headache, malaise, mild fever, puffiness around the eyes and face, flank pain, and oliguria. Hematuria is usually noted as "bloody" or, if the urine is acid, as "brown" or "coca-cola-colored." There may be moderate tachycardia, dyspnea, and moderate to marked elevation of blood pressure. Tenderness in the costovertebral angle is common.

2. Laboratory findings—The diagnosis is confirmed by examination of the urine, which may be grossly bloody or coffee-colored (acid hematin) or may show only microscopic hematuria. In addition, the urine contains protein (1–3+) and casts. Hyaline and granular casts are commonly found in large numbers, but the classic sign of glomerulitis, occasionally noted, is the erythrocyte cast. The erythrocyte cast is usually of small caliber, is intensely orange or red, and may show the mosaic pattern of the packed erythrocytes held together by the clot of fibrin and plasma protein.

With the impairment of renal function (decrease in glomerular filtration rate and blood flow) and with oliguria, plasma or serum urea nitrogen and creatinine become elevated, the levels varying with the severity of the renal lesion. A mild normochromic anemia may result from fluid retention and dilution.

Infection of the throat with nephritogenic streptococci is frequently followed by increasing antistreptolysin O titers in the serum, whereas high titers rarely are demonstrable following skin infections. The streptozyme test is available, consisting of five antistreptococcal antibodies, and has a diagnostic yield of 95% among those with pharyngitis and 80% of those with a skin infection as precipitating events. Serum complement levels (C3, C4, CH50 activity) are usually low.

The diagnosis is confirmed by examination of the urine, although the history and clinical findings in typical cases leave little doubt. The finding of erythrocytes in a cast is proof that erythrocytes were present in the renal tubules and did not arise from elsewhere in the genitourinary tract.

3. Microbiologic cultures—Because of the lag in symptoms weeks after the antecedent infection, only 25% of patients will have positive throat or skin cultures.

4. Renal biopsy—This is often not necessary; however, if the pattern of presentation deviates significantly from expected, a tissue diagnosis may help differentiate between differential diagnoses. For example, recurrent hematuria may indicate IgA nephropathy, whereas a persistently depressed complement (C3) level 6 weeks and beyond suggests a diagnosis of membrano-proliferative glomerulonephritis.

5. Treatment—There is no specific treatment. Eradication of infection, prevention of overhydration and hypertension, and prompt treatment of complications such as hypertensive encephalopathy and heart failure require careful management. Some have used intravenous (IV) methylprednisolone in patients with significant crescents at biopsy, but this is not a universal practice.

6. Prognosis—Most patients with the acute disease recover completely; 5–20% show progressive renal damage. This damage may be evident only years after the immune injury. If oliguria, heart failure, or hypertensive encephalopathy is severe, death may occur during the acute attack. Even with severe acute disease, however, recovery is the rule, particularly in children.

Immunoglobulin A Nephropathy

Primary hematuria (idiopathic benign and recurrent hematuria, Berger's disease) is now known to be an immune complex glomerulopathy in which deposition of IgA occurs in a granular pattern in the mesangium of the glomerulus. The associated light microscopic findings are variable and range from normal to extensive crescentic glomerulonephritis.

Recurrent macroscopic and microscopic hematuria and mild proteinuria are usually the only manifestations of renal disease. Most patients with IgA nephropathy are between the ages of 16 and 35 years at the time of diagnosis. The disease occurs much more frequently in males than in females and is the most common cause of glomerulonephritis among Asians and in the developed world. While most patients continue to have episodes of gross hematuria or microscopic hematuria, renal function is likely to remain stable. However, approximately 30% of patients will have progressive renal dysfunction and develop end-stage renal disease. Clinical features that indicate a poor prognosis include male sex, older age at onset of disease, the presence of nephrotic range proteinuria, hypertension, or renal dysfunction at presentation.

There is no satisfactory therapy for IgA nephropathy. Use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockade to lower proteinuria and delay progression of chronic kidney disease should be first-line therapy. The role of immunosuppressive drugs such as steroids and cytotoxic agents is not clear, and there have been few rigorously performed controlled trials. The STOP-IgAN investigators reported their findings showing that those treated with corticosteroids had a statistically significant higher complete remission rate (17% vs 5%, $p = .01$) than those on conversative therapy (ACE inhibitors/angiotensin receptor blockade). Overall, however, there was no difference in the rate of annual decline in renal function between groups. Patients treated with corticosteroid experienced higher adverse effects. A more intriguing approach is the use of omega-3 fatty acids (fish oils) to delay progression of the renal disease. A large, prospective, randomized, placebo-controlled trial in patients with IgA nephropathy using 12 g of omega-3 fatty acids has shown that fish oils probably can reduce the deterioration of renal function and the number of patients in whom end-stage renal disease develops.

After renal transplantation, recurrent IgA disease has been described. The risk varies from 21% to 58%. Of those who develop graft dysfunction attributable to recurrence, eventual graft loss occurred in 46–71% of patients. It is disputable whether allografts from living related donors confer a greater risk of recurrence than deceased or living unrelated donors.

Rapidly Progressive Glomerulonephritis

This condition is characterized by several pulmonary–renal diseases. The patient usually gives a history of recent hemoptysis and often of malaise, anorexia, and headache. A severe acute glomerulonephritis may be accompanied by diffuse hemorrhagic inflammation of the lungs. The urine shows gross or microscopic hematuria, and laboratory findings of severely suppressed renal function are usually evident. Biopsy shows glomerular crescents, glomerular adhesions, and inflammatory infiltration interstitially. Electron microscope examination shows an increase in basement membrane material and deposition of fibrin beneath the capillary endothelium. In cases of anti-GBM disease, circulating antibody against GBM can be identified. IgG, C3, and, often, other components of the classic complement pathway can be demonstrated as linear deposits on the basement membranes of the glomeruli and the lung. This was formerly called **Goodpasture's disease**.

Large doses of corticosteroids in combination with immunosuppressive therapy may be useful. Plasmapheresis to remove circulating antibody has been reported effective in some patients. Transplantation should be delayed until circulating antiglomerular basement antibodies have disappeared.

In contrast, some patients have crescenteric glomerulonephritis but do not show any immune deposits or antibody deposition by immunofluorescence studies. They have pauci-immune idiopathic rapidly progressive glomerulonephritis (RPGN). Many of these patients are serologically ANCA-positive. High-dose prednisone pulse therapy and cytotoxic agents may result in prolonged remission.

NEPHROTIC SYNDROME

Essentials of Diagnosis and General Considerations

- Edema
- Proteinuria >3.5 g/day
- Hypoalbuminemia <3 g/dL
- Hyperlipidemia: cholesterol >300 mg/dL
- Lipiduria: free fat, oval fat bodies, fatty casts

Because treatment and prognosis vary with the cause of nephrotic syndrome, renal biopsy is important. Light microscopy, electron microscopy, and immunofluorescence identification of immune mechanisms diagnose most causes of nephrosis.

Glomerular diseases associated with nephrosis include the lesions described in the following paragraphs.

Minimal Glomerular Lesions

Minimal-change nephropathy (nil disease) accounts for about 20% of cases of nephrosis in adults and 90% in children. No abnormality is visible by examination of biopsy material with the light microscope. With the electron microscope, alterations of the GBM, with effacement of foot processes of the epithelial cells, are evident. There is no evidence of immune disease by immunofluorescence studies. The response to treatment with corticosteroids is good, especially in children; however, in adults, a longer course of prednisone is normally required compared with the pediatric population. For patients who have frequent relapses with steroids or are steroid resistant, a course of cyclophosphamide or chlorambucil may induce a prolonged remission. Patients who do not respond to these agents may show a favorable response with cyclosporine or tacrolimus. Renal function usually remains stable. Partial response is uncommon, which should prompt a search for misdiagnosed FSGS due to sampling error on biopsy.

Focal Segmental Glomerulosclerosis (FSGS)

Focal segmental glomerulosclerosis (FSGS) is the second most common cause of nephrotic syndrome in children and an increasing cause of the nephrotic syndrome in adults. Some regard this to be in the same spectrum of disease as minimal change nephropathy. The diagnosis is based on light microscope findings of segmental hyalinosis and sclerosis associated with effacement of the foot processes on electron microscopy. Focal glomerulosclerosis is frequently idiopathic but can be associated with human immunodeficiency virus infection and heroin use. There is much debate about a circulating permeability factor as the causative agent, but its exact identity has remained elusive. Despite the discovery of an antibody directed against the soluble urokinase plasminogen activator Receptor (suPAR) as a potential culprit for post-transplant recurrent FSGS, there remains conflicting evidence. A secondary form of focal glomerulosclerosis without the diffuse changes in foot processes may occur in patients with a solitary kidney, hyperfiltration syndromes, and reflux nephropathy. There are reports of familial variants (due to nephrin and podocin mutations). The response of the idiopathic form of focal glomerulosclerosis to therapy is suboptimal. Prolonged corticosteroid therapy produces remission in approximately 40% of patients. Over a 10-year period, approximately 50% of patients will develop chronic kidney disease. Idiopathic focal glomerulosclerosis has a recurrence rate of 25% after transplantation. With a history of recurrence in a prior failed transplant, the risk of recurrence in a second transplant increases substantially.

Membranous Nephropathy

Examination of biopsy material with the light microscope shows thickening of the glomerular cells but no cellular proliferation. With the electron microscope, irregular lumpy deposits appear between the basement membrane and the epithelial cells, and new basement membrane material protrudes from the GBM as spikes or domes. Immunofluorescence studies show diffuse granular deposits of Ig (especially IgG) and complement (C3 component). As the membrane thickens, glomeruli become sclerosed and hyalinized.

The pathogenesis of most cases of membranous nephropathy in humans is unclear. Several mechanisms have been suggested. They include trapping of circulating immune complexes or binding of an antibody to scattered glomerular antigens (either present already or "planted" after a nonrenal-source antigen lodges in the glomerulus). Excitement over the discovery of the M-type phospholipase A_2 receptor antibody as a marker of primary/idiopathic membranous GN established this as an autoimmune condition.

There is considerable controversy regarding the effectiveness of therapy with steroids or immunosuppressive agents. Therapy should be used most often in patients with high risk of progressive renal failure with the following criteria: proteinuria >5 g/day, hypertension, and elevated serum creatinine. Initial protocols consisted of using prednisone/methylprednisolone and chlorambucil (so called Ponticelli protocol), but head-to-head trials showed equal outcomes with cyclophosphamide, which is preferred given the multitude of side effects with chlorambucil.

Membranoproliferative Glomerulonephritis—Types I and II

In type I MPGN, light microscopy shows thickening of glomerular capillaries, accompanied by mesangial proliferation and obliteration of glomeruli. Some cases show the characteristic double-contour glomerular capillary membranes. With the electron microscope, subendothelial deposits and growth of mesangium into capillary walls are demonstrable. Immunofluorescence studies show the presence of C3 component of complement and, rarely, Ig. The most common cause of MPGN type I is chronic hepatitis C virus infection. This condition is usually associated with high levels of IgG/IgM. Cryoimmunoglobulins may be present with normal or slightly reduced levels of complement. There is no known effective treatment. Traditionally, treatment of hepatitis C using pegylated interferon-α and ribavirin (in those with eGFR >50 mL/min) may slow down progression or prompt regression of renal lesions. Newer direct acting antiviral agents in the armamentarium of hepatitis C treatment has dramatically increased eradication rates and ameliorate its effect on renal function.

Type II MPGN is characterized by dense deposits visible by electron microscopy and lack of findings by immunofluorescence studies. Treatment is unsatisfactory, and there is a high rate of recurrence after kidney transplantation (80–100%).

Miscellaneous Diseases

Many medical illnesses that are metabolic, autoimmune, or infectious, as well as neoplastic diseases and reactions to drugs and other toxic substances can produce glomerular disease. These include diabetic glomerulopathy, systemic lupus erythematosus, ANCA-positive renal disease (including GPA), amyloid disease, multiple myeloma, lymphomas, carcinomas, syphilis, reaction to toxins, reaction to drugs (eg, trimethadione), and exposure to heavy metals.

Another rare glomerular illness that causes nephrotic syndrome is fibrillary and immunotactoid glomerular nephritis. The lesions of fibrillary glomerulonephritis are characterized by randomly oriented fibril deposits 10–30 nm in diameter located within the mesangium and capillary wall. Immunotactoid glomerulopathy is characterized by deposits of microtubular structures of 18–19 nm and has been associated with lymphoproliferative disorders. In contrast to amyloid, the deposits in both diseases are Congo red-negative. Treatment is generally unsatisfactory.

Clinical Findings in Nephrosis

A. Symptoms and Signs

Edema may appear insidiously and increase slowly or can appear suddenly and accumulate rapidly. Symptoms other than those related to the mechanical effects of edema are not remarkable.

On physical examination, massive peripheral edema is apparent. Signs of hydrothorax and ascites are common. Pallor is often accentuated by the edema, and striae commonly appear.

B. Laboratory Findings

The urine contains large amounts of protein, 4–10 g per ≥24 hours. There is a good correlation between the urine protein: creatinine ratio (from a “spot” morning urine) and the 24-hour urine collections. For example, a ratio in excess of 3:1 in the spot urine usually correlates to a 24-hour proteinuria of 3 g. The sediment contains casts, including the characteristic fatty and waxy varieties; renal tubular cells, some of which contain fatty droplets (oval fat bodies); and variable numbers of erythrocytes. A mild normochromic anemia is common, but anemia may be more severe if renal damage is great. Nitrogen retention varies with the severity of impairment of renal function. The plasma is often lipemic, and the blood cholesterol is usually greatly elevated. Plasma protein is greatly reduced. The albumin fraction may fall to <2 g/dL. Serum complement is usually low in active disease. The serum electrolyte concentrations are often normal, although the serum sodium may be slightly low; total serum calcium may be low, in keeping with the degree of hypoalbuminemia and decrease in the protein-bound calcium moiety. During edema-forming periods, urinary sodium excretion is very low and urinary aldosterone excretion is elevated. If renal insufficiency (see preceding discussion) is present, the blood and urine findings are usually altered accordingly.

Renal biopsy is often essential to establish the diagnosis between the various conditions and to indicate prognosis.

C. Differential Diagnosis

The nephrotic syndrome (nephrosis) may be associated with a variety of primary renal diseases or may be secondary to a systemic process: collagen–vascular diseases (eg, disseminated lupus erythematosus, polyarteritis), diabetic nephropathy, amyloid disease, thrombosis of the renal vein, myxedema, multiple myeloma, malaria, syphilis, reaction to toxins or heavy metals, reactions to drugs, and constrictive pericarditis.

D. Treatment

An adequate diet with restricted sodium intake (0.5–1 g/day) and prompt treatment of intercurrent infection are the basis of therapy. Diuretics may be given but are often only partially effective. Salt-free albumin and other oncotic agents are of little help, and their effects are transient. The corticosteroids have been shown to be of value in treating nephrotic syndrome when the underlying disease is of minimal change—focal segmental glomerulosclerosis, systemic lupus erythematosus, or proliferative and crescentic glomerulonephritis. Steroids are often less effective in the treatment of membranous disease and membranoproliferative lesions of the glomerulus.

Alkylating agents, azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus have been used in the treatment of nephrotic syndrome. Encouraging early results have been reported in children and adults with proliferative or membranous lesions and with systemic lupus erythematosus. It is not known what percentage of patients can be expected to benefit from these drugs.

Both corticosteroids and cytotoxic agents are commonly associated with serious side effects. At present, this form of therapy should be employed only in patients in whom the disease has proved refractory to well-established treatment regimens.

Reduction in proteinuria and improvement in nephrotic edema have been reported using low-protein diets and ACE inhibitors or angiotensin receptor blockers (ARBs). Most recently, studies have shown some improvements with lipid-lowering drugs.

E. Prognosis

The course and prognosis depend on the basic disease responsible for the nephrotic syndrome. In most children with nephrosis (usually secondary to minimal change nephropathy), the disease appears to run a rather benign course when properly treated and to leave insignificant sequelae. Of the remaining children, most go inexorably into renal insufficiency. Adults with nephrosis fare less well. Hypertension, heavy proteinuria, and renal dysfunction are poor prognosticators.

RENAL INVOLVEMENT IN COLLAGEN DISEASES

Although it may not be accurate to classify all of these disorders as collagen diseases, systemic lupus erythematosus, polyarteritis nodosa, microscopic angiitis, scleroderma, GPA, Henoch–Schönlein purpura, and thrombotic thrombocytopenic purpura have been implicated in cases of glomerulonephritis. The urine sediment is often diagnostic, containing erythrocytes and erythrocyte casts; renal tubular cells, including some filled with fat droplets; and waxy and granular broad casts. The presence of these formed elements is indicative of active glomerular and tubular disease. The symptoms and signs of the primary disease, involving extrarenal findings (eg, pulmonary or ear, nose, or throat changes with GPA; dermatologic abnormalities or carditis with systemic lupus erythematosus; dysphagia with scleroderma), as well as the presence of ANCA and other serologic tests, help to differentiate the form of collagen disease present. Complete renal recovery from the disease is not likely to occur, although steroid and immunosuppressive drugs (alone or in combination) may be effective for long-term amelioration.

DISEASES OF THE RENAL TUBULES AND INTERSTITIUM

Interstitial Nephritis

Acute interstitial diseases are usually due to sensitivity to drugs, including antibiotics (penicillin, sulfonamides), nonsteroidal anti-inflammatory drugs, and phenytoin. The pathologic hallmark of acute interstitial nephritis is the infiltration of inflammatory cells in the interstitium. A typical presentation is a rapid deterioration in renal function associated with a recent introduction of a new drug. The finding of eosinophiluria is very suggestive of allergic interstitial nephritis. Recovery may be complete, especially if the offending drug is withdrawn. A short course with corticosteroids may hasten the recovery.

Chronic interstitial nephritis is characterized by focal or diffuse interstitial fibrosis accompanied by infiltration, with inflammatory cells ultimately associated with extensive tubular atrophy. It represents a nonspecific reaction to a variety of causes: analgesic abuse, lead and cadmium toxicity, nephrocalcinosis, urate nephropathy, radiation nephritis, sarcoidosis, Balkan nephritis, and some instances of obstructive uropathy.

Analgesic Nephropathy

Analgesic nephropathy typically occurs in patients with chronic and recurrent headaches or with chronic arthritis who habitually consume large amounts of the drugs. Phenacetin was implicated initially, but with elimination of phenacetin from the mixtures, the incidence of analgesic nephropathy has not decreased. Chronic use of nonsteroidal anti-inflammatories is a frequent cause of this condition. The ensuing damage to the kidneys usually is detected late, after renal insufficiency has developed. Careful history taking or the detection of analgesic metabolites in the urine can lead to this diagnosis. The history of excessive use of analgesics may be concealed by the patient. The effects of the drug appear to be cumulative (ie, lifetime total dose of intake).

The kidney lesion is pathologically nonspecific, consisting of peritubular and perivascular inflammation with degenerative changes of the tubular cells (chronic interstitial nephritis). There are often no glomerular changes. Renal papillary necrosis extending into the medulla may involve many papillae.

Hematuria can be a common presenting complaint, but it is usually microscopic. Renal colic occurs when necrotic renal papillae slough away. Polyuria may be prominent. Signs of acidosis (hyperpnea), dehydration, and pallor are common. Infection is a frequent complication. The urine usually is remarkable only for the presence of blood and small amounts of protein. Elevated blood urea nitrogen (BUN) and creatinine and the electrolyte changes characteristic of metabolic acidosis and renal failure are typically present. Urinary concentrating impairments are usually present. Urograms show cavities and ring shadows typical of areas of destruction of papillae.

Uric Acid Nephropathy

Crystals of urate produce an interstitial inflammatory reaction. Urate may precipitate out in acid urine in the calyces to form uric acid stones. Patients with myeloproliferative disease under treatment are subject to occlusion of the upper urinary tract by uric acid crystals (tumor lysis syndrome). Alkalinization of the urine and a liberal fluid intake help prevent crystal formation. Allopurinol is a useful drug to prevent hyperuricemia and hyperuricosuria. Recombinant urate oxidase (rasburicase) has been used in those with severe tumor lysis syndrome to lower the uric acid load.

Recently, it has been suggested that many instances considered to be chronic "gouty nephropathy" are instead related to chronic lead renal injury and are not due to primary uric acid depositions.

Obstructive Uropathy

Interstitial nephritis due to obstruction may not be associated with infection. Tubular conservation of salt and water is impaired. Partial to full renal recovery follows relief of the obstruction but is inversely related to the duration of obstruction.

Kidney Diseases in Multiple Myeloma

Features of myelomatosis that contribute to renal disease include proteinuria (including filterable Bence Jones protein and κ and λ chains) with precipitation in the tubules leading to accumulation of abnormal proteins in the tubular lumen. A Fanconi-like syndrome may develop.

Plugging of tubules, tubular atrophy, and, occasionally, the accumulation of amyloid may also be present. Renal failure may occur acutely or develop slowly. Hemodialysis may rescue the patient during efforts to control the myeloma with chemical agents.

Another related primary renal disorder is termed **light-chain deposition disease**. Patients have nephritic range proteinuria and usually progressive renal failure. In contrast to multiple myeloma, there is no malignant hematopoietic process. Either κ or λ light chains are measurable via urine and serum immunofixation studies. Light-chain deposits are seen in the glomeruli. There is no effective treatment.

HEREDITARY RENAL DISEASES

The importance of inheritance and the familial incidence of disease warrant the inclusion of a classification of hereditary renal diseases. Although it is relatively uncommon in the population at large, hereditary renal disease must be recognized to permit early diagnosis for detection and genetic counseling.

Chronic Hereditary Nephritis

Evidence of the disease usually appears in childhood, with episodes of hematuria. Renal insufficiency commonly develops in males but only rarely in females. Survival beyond age 40 years is rare.

In many families, deafness and abnormalities of the eyes accompany the renal disease (so-called Alport disease). Another form of the disease is accompanied by polyneuropathy. Infection of the urinary tract is a common complication.

There is splitting and thickening of the GBM or podocyte proliferation and thickening of Bowman's capsule. Recently, kindreds have been described that have "thin-membrane disease." This condition is characterized by microscopic hematuria and, often, later progression to chronic renal failure. This, like Alport disease, may represent inherited abnormalities or deficiencies in type IV collagen in the GBM. This affects both genders. Therefore, it is generally inadvisable to accept female relatives of male Alport recipients who are found to have urinary abnormalities or documented thin basement membrane as living kidney donors.

Laboratory findings with these conditions are commensurate with existing renal function. Treatment is symptomatic.

Cystic Diseases of the Kidney

Congenital structural anomalies of the kidney must be considered in any patient with hypertension, pyelonephritis, or renal insufficiency. Many of these patients are at increased risk of urinary tract infection.

A. Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Autosomal dominant polycystic kidney disease (ADPKD) is familial and often involves not only the kidney but the liver and pancreas as well. It is clear that at least two genetic loci can lead to autosomal dominant polycystic kidney disease (PKD1 and PKD2 genes).

The formation of cysts on the cortex of the kidney is thought to result from failure of union of the collecting tubules and convoluted tubules of some nephrons. Intrarenal cysts may be of a proximal or a distal luminal type, differing on analysis by their cyst electrolyte content. This is important if one or more of these cysts become infected, and an antibiotic (with varying cyst-type penetrance) is chosen. New cysts do not form, but those present enlarge and, by exerting pressure, cause destruction of adjacent renal tissue. The incidence of cerebral vessel aneurysms and mitral valve prolapse is higher than normal.

Cases of ADPKD are discovered during the investigation of hypertension, by diagnostic study in patients presenting with pyelonephritis or hematuria, or by investigation of families of patients with known polycystic disease. At times, flank pain due to hemorrhage into a cyst occurs. Otherwise the symptoms and signs are those commonly seen in hypertension or renal insufficiency. On physical examination, the enlarged, irregular kidneys are often easily palpable.

The urine may contain leukocytes and erythrocytes. With bleeding into the cysts, there may also be bleeding into the urinary tract. The blood chemistry findings reflect the degree of renal insufficiency. Examination by sonography, CT scan, or x-ray shows the enlarged kidneys, and urography demonstrates the classic elongated calyces and renal pelvises stretched over the surface of the cysts. Researchers have established ultrasonographic criteria for the diagnosis of autosomal dominant polycystic kidney disease (when genetic testing is not available or unknown genotype). (See Table 33–1.)

No specific therapy is available, and surgical interference is indicated only to decompress very large cysts in patients with severe pain. Initial excitement with mTOR inhibitors in limiting cyst growth did not translate into improved renal function in recent studies, dampening enthusiasm for its clinical applicability. FDA just approved the use of a vasopressin-2 receptor antagonist, tolvaptan, in the treatment of ADPKD. Clinical studies have shown better preservation of renal function, with a treatment effect of (1.3 mL/min)/(1.73 m^2/year) in the tolvaptan group). Total kidney volume growth was also found to be lower in the tolvaptan versus placebo groups (2.8% vs 5.5% per year). There appeared to

Table 33–1. Ultrasonographic criteria for the diagnosis of autosomal dominant polycystic kidney disease.

Age (years)	Diagnostic criteria	Sensitivity	Specificity
15–29	Three unilateral/ bilateral cysts	82	100
30–39	Three unilateral/ bilateral cysts	96	100
40–59	Two cysts in each kidney	90	100
>60	Four cysts in each kidney	100	100

Data from Pei Y, Obaji J, Dupuis A, et al: Unified criteria for ultrasonographic diagnosis of ADPKD, J Am Soc Nephrol. 2009 Jan;20(1):205–212.

be a higher incidence of transaminitis in the tolvaptan group that requires regular monitoring during the course of therapy.

Patients with polycystic kidney disease live in reasonable comfort with slowly advancing uremia. Both hemodialysis and renal transplantation extend the life of these patients. Nephrectomy is indicated only in patients with recurrent infections, severe recurrent bleeding, or markedly enlarged kidneys causing compressive symptoms.

B. Cystic Disease of the Renal Medulla

1. Medullary cystic disease—Medullary cystic disease is a familial disease that may become symptomatic during adolescence. Anemia is usually the initial manifestation, but azotemia, acidosis, and hyperphosphatemia soon become evident. Urine findings are not remarkable, although there is often an inability to concentrate, and renal salt wasting often occurs. Many small cysts are scattered through the renal medulla. Renal transplantation is indicated by the usual criteria.

2. Medullary sponge kidney—Medullary sponge kidney is asymptomatic and is discovered by the characteristic appearance of tubular ectasia in the urogram. Enlargement of the papillae and calyces and small cavities within the pyramids is demonstrated by the contrast media in the excretory urogram. Many small calculi often occupy the cysts, and infection may be troublesome. Life expectancy is not affected, and only therapy for ureteral stone or for infection is required.

ANOMALIES OF THE PROXIMAL TUBULE

▶ Defects of Amino Acid Reabsorption

A. Congenital Cystinuria

Increased excretion of cystine results in the formation of cystine calculi in the urinary tract. Ornithine, arginine, and lysine are also excreted in abnormally large quantities. There is also a defect in absorption of these amino acids in the jejunum. Nonopaque stones should be examined chemically to provide a specific diagnosis.

Treatment goals include a large fluid intake and keeping the urine pH above 7 by giving sodium bicarbonate and sodium citrate plus acetazolamide at bedtime to ensure an alkaline night urine. In refractory cases, a low-methionine (cystine precursor) diet may be necessary. Penicillamine has proved useful in some cases.

B. Aminoaciduria

Many amino acids may be poorly absorbed, resulting in unusual losses. Failure to thrive and the presence of other tubular deficits suggest the diagnosis. There is no treatment.

C. Hepatolenticular Degeneration (Wilson's Disease)

In this congenital familial disease, aminoaciduria and renal tubular acidosis (RTA) are associated with cirrhosis of the liver and neurologic manifestations. Hepatomegaly, evidence of impaired liver function, spasticity, athetosis, emotional disturbances, and Kayser–Fleischer rings around the cornea constitute a unique syndrome. There is a decrease in synthesis of ceruloplasmin, with a deficit of plasma ceruloplasmin and an increase in free copper that may be etiologically specific.

Penicillamine is given to chelate and remove excess copper. Edathamil (EDTA) may also be used to remove copper.

D. Multiple Defects of Tubular Function (de Toni–Fanconi–Debré Syndrome)

Aminoaciduria, phosphaturia, glycosuria, and a variable degree of RTA characterize this syndrome. Osteomalacia is a prominent clinical feature; other clinical and laboratory manifestations are associated with specific tubular defects described previously.

Treatment consists of replacing cation deficits (especially potassium), correcting acidosis with bicarbonate or citrate, replacing phosphate loss with isoionic neutral phosphate (mono- and disodium salts) solution, and ensuring a liberal calcium intake. Vitamin D is useful, but the dose must be controlled by monitoring levels of serum calcium and phosphate.

E. Defects of Phosphorus and Calcium Reabsorption

Several sporadic, genetically transmitted, and acquired disorders are grouped under this category and are characterized by persisting hypophosphatemia because of excessive phosphaturia and an associated metabolic bone disorder, rickets in childhood, and osteomalacia in adulthood. Response to vitamin D therapy (1, 25-dihydroxycholecalciferol, the active analog of vitamin D) is variable.

F. Defects of Glucose Absorption (Renal Glycosuria)

Renal glycosuria results from an abnormally poor ability to reabsorb glucose and is present when blood glucose levels are normal. Ketosis is not present. The glucose tolerance response is normal. There is no treatment for renal glycosuria, only reassurance.

G. Defects of Bicarbonate Reabsorption

Proximal RTA, type II, is due to reduced bicarbonate reclamation in the proximal tubule, with resultant loss of bicarbonate in the urine and decreased bicarbonate concentration in extracellular fluid. There are increased K^+ losses into the urine and retrieval of Cl^- instead of HCO_3. The acidosis is therefore associated with hypokalemia and hyperchloremia. Transport of glucose, amino acids, phosphate, and urate may be deficient as well (Fanconi syndrome).

ANOMALIES OF THE DISTAL TUBULE

Defects of Hydrogen Ion Secretion and Bicarbonate Reabsorption (Classic Renal Tubular Acidosis, Type I)

Failure to secrete hydrogen ion and to form ammonium ion results in loss of "fixed base," sodium, potassium, and calcium. There is also a high rate of phosphate excretion. Vomiting, poor growth, and symptoms and signs of chronic metabolic acidosis are accompanied by weakness due to potassium deficit and bone discomfort due to osteomalacia. Nephrocalcinosis, with calcification in the medullary portions of the kidney, occurs in about one-half of cases. The urine is alkaline and contains larger-than-normal quantities of sodium, potassium, calcium, and phosphate. An abnormality in urinary anion gap ($U{\bullet}Na^+ + U{\bullet}K^+ - U{\bullet}Cl^-$) is noted (low), which is associated with the reduced NH_4^+ production. This abnormality differentiates this condition from type II RTA and from the metabolic acidosis seen with diarrhea. The blood chemistry findings are those of metabolic acidosis with low serum potassium.

Treatment consists of replacing deficits and increasing the intake of sodium, potassium, calcium, and phosphorus. Sodium and potassium should be given as bicarbonate or citrate. Additional vitamin D may be required.

Excess Potassium Secretion (Potassium "Wastage" Syndrome)

Excessive renal secretion or loss of potassium may occur in four situations: (1) moderate renal insufficiency with diminished H^+ secretion; (2) RTA (proximal and distal RTA); (3) hyperaldosteronism and hyperadrenocorticism; or (4) tubular secretion of potassium, the cause of which is unknown. Hypokalemia indicates that the deficit is severe. Muscle weakness and polyuria and dilute urine are signs attributable to hypokalemia. Treatment consists of correcting the primary disease and giving supplementary potassium.

Reduced Potassium Secretion

Reduced potassium secretion is noted in conditions in which extrarenal aldosterone is reduced or when intrarenal production of renin (and secondary hypoaldosteronism) occurs. The latter condition is termed **RTA, type IV**, and is associated with impaired H^+ and K^+ secretion in the distal tubule. Drug-induced interstitial nephritis, gout, and diabetes mellitus are clinical circumstances that may produce type IV RTA and resulting hyperkalemia and mild metabolic acidosis. Treatment consists in promoting kaliuresis (with loop diuretics), prescribing potassium-binding gastrointestinal resins (Kayexalate [sodium polystyrene sulfonate]), or providing the patient with a mineralocorticoid, fludrocortisone acetate.

Defects of Water Absorption (Renal Diabetes Insipidus)

Nephrogenic diabetes insipidus occurs more frequently in males than in females. Unresponsiveness to antidiuretic hormone is the key to differentiate from central (pituitary) diabetes insipidus.

In addition to congenital refractoriness to antidiuretic hormone, obstructive uropathy, lithium, methoxyflurane, and demeclocycline also may render the tubule refractory to vasopressin.

Symptoms are related to inability to reabsorb water, with resultant polyuria and polydipsia. The urine volume approaches 12 L/day, and osmolality and specific gravity are low.

Treatment consists primarily of an adequate water intake. Chlorothiazide may ameliorate the polyuria; the mechanism of action is unknown, but the drug may act by increasing isosmotic reabsorption in the proximal segment of the tubule.

UNSPECIFIED RENAL TUBULAR ABNORMALITIES

In idiopathic hypercalciuria, decreased reabsorption of calcium predisposes to the formation of renal calculi. Serum calcium and phosphorus are normal. Urine calcium excretion is high; urine phosphorus excretion is low. Microscopic hematuria may be present. For treatment of urinary stones containing calcium, see Chapter 17, on urinary stone disease.

BIBLIOGRAPHY

Adler S: Diabetic nephropathy: Linking histology, cell biology, and genetics. Kidney Int 2004;66:2095.

Afshin P, Kao L, Xie D, et al: APOL1 risk variants, race, and progression of chronic kidney disease. New Engl J Med 2013;369(23):2183–2196.

Alric L et al: Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. Am J Kidney Dis 2004;43:617.

Anonymous: Imaging the kidney—radiologic imaging 2006. (Excerpts) Nephron Clin Pract 2006;103:c19.

Appel GB et al: Membranoproliferative glomerulonephritis type II (dense deposit disease): An update. J Am Soc Nephrol 2005;16:1392.

Barratt J, Feehally J: IgA nephropathy. J Am Soc Nephrol 2005;16:2088.

Braden GL et al: Tubulointerstitial diseases. Am J Kidney Dis 2005; 46:560.

Buhaescu I et al: Systemic vasculitis: Still a challenging disease. Am J Kidney Dis 2005;46:173.

Chesney R: The changing face of childhood nephrotic syndrome. Kidney Int 2004;66:1294.

Couser WG (guest editor): Frontiers in nephrology: Membranous nephropathy. J Am Soc Nephrol 2005;16:1184.

Flanc RS et al: Treatment of diffuse proliferative lupus nephritis: A meta-analysis of randomized controlled trials. Am J Kidney Dis 2004;43:197.

Ginzler EM et al: Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. New Engl J Med 2005;353:2219.

Grantham JJ: Advancement in the understanding of polycystic kidney disease: A system approach. Kidney Int 2003;64:1154.

Heering P et al: Cyclosporine A and chlorambucil in the treatment of idiopathic focal segmental glomerulosclerosis. Am J Kidney Dis 2004;43:10.

Hofstra JM, Wetzels JFM: Phospholipase A2 receptor antibodies in membranous nephropathy: Unresolved issues. J Am Soc Nephrol 2014;25(6):1137–1139.

Hruska KA: Treatment of chronic tubulointerstitial disease: A new concept. Kidney Int 2002;61:1911.

Izzedine H et al: Oculorenal manifestations in systemic autoimmune diseases. Am J Kidney Dis 2004;43:209.

Javaid B, Quigg RJ: Treatment of glomerulonephritis: Will we ever have options other than steroids and cytotoxics? Kidney Int 2005; 67:1692.

McGarth MM, Isakova T, Rennke H, et al: Contaminated cocaine and anti-neutrophilic cytoplasmic antibody-associated disease. Clin J Am Soc Nephrol 2011;6(12):2799–2805.

Nair R, Walker PD: Is IgA nephropathy the commonest primary glomerulopathy among young adults in the USA? Kidney Int 2006;69:1455.

Noris M, Remuzzi G: Hemolytic uremic syndrome. J Am Soc Nephrol 2005;16:1035.

Perna A et al: Immunosuppressive treatment for idiopathic membranous nephropathy: A systematic review. Am J Kidney Dis 2004; 44:385.

Pettitt DJ et al: Familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1990;33(7):438–443.

Ponticelli C et al: A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol 1998;9(3):444–450.

Rauen T, Eitner F, Fitzner C, et al: Intensive supportive care plus immunosuppression in IgA nephropathy. New Engl J Med 2015; 373(23):2225–2236.

Rosner MH, Bolton WK: Renal function testing. Am J Kidney Dis 2006;47:174.

Rossert J: Drug-induced acute interstitial nephritis. Kidney Int 2001; 60:804.

Tenenhouse HS, Murer H: Disorders of renal tubular phosphate transport. J Am Soc Nephrol 2003;14:240.

Torres VE, Chapman AB, Devuyst O, et al: Tolvaptan in later-stage autosomal dominant polycystic kidney disease. New Engl J Med 2017;377(20):1930–1942.

Troyanov S et al: Renal pathology in idiopathic membranous nephropathy: A new perspective. Kidney Int 2006;69:1641.

Wilmer WA et al: Management of glomerular proteinuria: A commentary. J Am Soc Nephrol 2003;14:3217.

34

Acute Kidney Injury and Oliguria

Brian K. Lee, MD; & Flavio G. Vincenti, MD

Oliguria literally means "reduced" urine volume—less than that necessary to remove endogenous solute loads that are the end products of metabolism. If the patient concentrates urine in a normal fashion while consuming a regular Western diet, oliguria (for that person) is present at urine volumes of <400 mL/day, or approximately 6 mL/kg body weight. If the kidney concentration is impaired and the patient can achieve a specific gravity of only 1.010, oliguria is present at urine volumes of <1000–1500 mL/day.

To standardize the diagnosis of acute renal failure, the new term **acute kidney injury (AKI)** was coined. New staging systems have been devised to compare severity of the damage sustained across different study groups and for prognostication.

Acute kidney injury is a condition in which the glomerular filtration rate is abruptly reduced, causing a sudden retention of endogenous and exogenous metabolites (urea, potassium, phosphate, sulfate, creatinine, administered drugs) that are normally cleared by the kidneys. The urine volume is usually low (<400 mL/day). If renal concentrating mechanisms are impaired, the daily urine volume may be normal or even high (***high-output*** or ***nonoliguric renal failure***). In extreme cases, anuria occurs (urine output completely shuts down) in acute kidney injury.

The causes of AKI are listed in Table 34–1. Prerenal causes are usually reversible if treated promptly, but a delay in therapy may allow it to progress to a fixed intrinsic renal failure (eg, acute tubular necrosis). The other causes of AKI are classified according to their involvement with vascular lesions, intrarenal disorders, or postrenal disorders.

PRERENAL KIDNEY INJURY

The term ***prerenal*** denotes inadequate renal perfusion or lowered effective arterial circulation. The most common cause of this form of AKI is dehydration due to renal or extrarenal fluid losses from diarrhea, vomiting, excessive use of diuretics, and other systemic disturbances. Less common causes are septic shock, "third spacing" with extravascular fluid pooling (eg, pancreatitis), and excessive use of antihypertensive drugs. Heart failure with reduced cardiac output also can reduce effective renal blood flow. Careful clinical assessment may identify the primary condition responsible for the prerenal state, but several conditions often can coexist. In the hospital setting, these circulatory abnormalities often are prolonged, leading to a more sustained injury (acute tubular necrosis).

Acute reductions in glomerular filtration rate may also be noted in patients with cirrhosis (hepatorenal syndrome) or in patients taking cyclosporine, tacrolimus, nonsteroidal anti-inflammatory drugs, or angiotensin-converting enzyme (ACE) inhibitors. It is felt that these conditions represent significant intrarenal hemodynamic functional derangements. In these clinical circumstances, the urinary findings may mimic prerenal renal failure, but the patient's clinical assessment does not demonstrate the extrarenal findings seen in common prerenal conditions, as noted in the following section. Improvements in glomerular filtration rate are usually noted after drug discontinuance or, in cases of hepatorenal syndrome, with management of the liver disease or following liver transplantation.

Clinical Findings

A. Symptoms and Signs

Except for rare cases with associated cardiac or "pump" failure, patients usually complain of thirst or of dizziness in the upright posture (orthostatic dizziness). There may be a history of overt fluid loss. Weight losses reflect the degree of dehydration. Physical examination frequently reveals decreased skin turgor, collapsed neck veins, dry mucous membranes, and, most importantly, excessive orthostatic or postural changes in blood pressure (defined as a systolic drop of >20 or a diastolic drop of >10 mm Hg) and pulse.

Table 34–1. Causes of acute kidney injury.

- **Prerenal**
  - Dehydration
  - Vascular collapse due to sepsis, antihypertensive drug therapy, "third spacing"
  - Reduced cardiac output
- **Functional–hemodynamic**
  - Angiotensin-converting enzyme inhibitor drugs
  - Nonsteroidal anti-inflammatory drugs
  - Cyclosporine; tacrolimus (calcineurin inhibitors)
  - Hepatorenal syndrome
- **Vascular**
  - Atheroembolism
  - Dissecting arterial aneurysms
  - Malignant hypertension
- **Parenchymal (intrarenal)**
  - Specific
    - Glomerulonephritis
    - Interstitial nephritis
    - Toxin, dye-induced
    - Hemolytic uremic syndrome
  - Nonspecific
    - Acute tubular necrosis
    - Acute cortical necrosis
- **Postrenal**
  - Calculus in patients with solitary kidney
  - Bilateral ureteral obstruction
  - Outlet obstruction
  - Leak, posttraumatic

B. Laboratory Findings

1. Urine—The urine volume is usually low. Accurate assessment may require bladder catheterization followed by hourly output measurements (which will also rule out lower urinary tract obstruction; see discussion following). High urine specific gravity (>1.025) and urine osmolality (>600 mOsm/kg) are also noted in this form of acute apparent renal failure. Routine urinalysis usually shows a bland sediment. However, as it progresses to acute tubular necrosis, sloughed off tubular cells and muddy brown casts may become apparent.

2. Urine and blood chemistries—The blood urea nitrogen (BUN): creatinine ratio, normally 10:1, is usually increased with prerenal renal failure. Other findings are set forth in Table 34–2. Because mannitol, radiocontrast dyes, and diuretics affect the delivery and tubular handling of urea, sodium, and creatinine, the urine and blood chemistry tests performed after these agents have been given can be misleading.

3. Central venous pressure—A low central venous pressure indicates hypovolemia. If severe cardiac failure is the principal cause of prerenal renal failure (it is rarely the sole cause), reduced cardiac output and high central venous pressure are apparent.

Table 34–2. Intrinsic versus prerenal azotemia.

Parameter	Intrinsic	Prerenal
Urine osmolality (mOsm/L)	<350	>500
Urine/plasma urea	<3	>8
Urine/plasma creatinine	<20	>40
Urine Na (mEq/L)	>40	<20
$FE_{Na} = \frac{U/P_{Na}}{U/P_{cr}} \times 100$	>1	<1
$FE_{urea} = \frac{U/P_{urea}}{U/P_{cr}}$	>50	<35
$FE_{uric\,acid} = \frac{U/P_{uric\,acid}}{U/P_{cr}}$	>15	<7

Data from Miller TR, Anderson RJ, Linas SL, et al: Urinary diagnostic indices in acute renal failure: A prospective study. Ann Intern Med. 1978 Jul;89(1):47–50; Greenburg A, Cheung AK, Coffman TM, et al: Primer on Kidney Diseases, 4th ed. Philadelphia, PA: National Kidney Foundation/Elsevier Saunders; 2005.

4. Fluid challenge—An increase in urine output in response to a carefully administered fluid challenge is both diagnostic and therapeutic in cases of prerenal renal failure. Rapid intravenous administration of 300–500 mL of physiologic saline is the usual initial treatment. Urine output is measured over the subsequent 1–3 hours. A urine volume increase of >50 mL/h is considered a favorable response that warrants continued intravenous infusion. If the urine volume does not increase, the physician should carefully review the results of blood and urine chemistry tests, reassess the patient's fluid status, and repeat the physical examination to determine whether an additional fluid challenge (with or without furosemide) might be worthwhile.

▶ Treatment

In states of dehydration, fluid losses must be rapidly corrected to treat oliguria. Inadequate fluid management may cause further renal hemodynamic deterioration and eventual renal tubular ischemia (with fixed acute tubular necrosis; see discussion following below). If oliguria and hypotension persist in a well-hydrated patient, vasopressor drugs are indicated in an effort to correct the hypotension associated with sepsis or cardiogenic shock. Pressor agents that restore systemic blood pressure while maintaining renal blood flow and renal function are most useful. However, the previously touted benefits of renally dosed dopamine (1–5 μg/kg per minute) have not been proven. A more promising agent might be fenoldopam, a direct dopamine A_1 receptor agonist. However, this will have to be tested more rigorously in a randomized trial before it can be widely recommended.

Discontinuance of antihypertensive medications or diuretics can, by itself, cure the apparent acute kidney injury resulting from prerenal conditions.

VASCULAR RENAL FAILURE

Common causes of acute kidney injury due to vascular disease include atheroembolic disease, dissecting arterial aneurysms, and malignant hypertension. Atheroembolic disease is rare before age 60 years, and precipitating events include vascular procedures, angiographic studies, and administration of heparin anticoagulation. An insidious, subacute worsening of renal function over weeks following the inciting events is seen in most cases. Diagnosis is usually made from history and physical examination, including signs of peripheral atheroemboli such as blue toe syndrome, transient ischemic attack (TIA)/strokes, livedo reticularis, and mesenteric ischemic pain. Laboratory findings may reveal peripheral eosinophilia and hypocomplementemia. Renal biopsy, if performed, may show cholesterol clefts. No definitive treatments are available, except for risk reduction of further embolization, and supportive care. Observational studies suggest potential benefits from statin use (the relative risk for composite outcome of death or end-stage renal disease was 0.53). Dissecting arterial aneurysms and malignant hypertension are usually clinically evident.

Rapid assessment of the arterial blood supply to the kidney requires arteriography or other noncontrasted blood flow studies (eg, magnetic resonance imaging or Doppler ultrasound). The cause of malignant hypertension may be identified on physical examination (eg, scleroderma). Primary management of the vascular process is necessary to affect the course of these forms of acute kidney injury.

INTRARENAL CAUSES

Diseases in this category can be divided into specific and nonspecific parenchymal processes.

Regarding **specific intrarenal disease states**, the most common causes of acute kidney injury are acute or rapidly progressive glomerulonephritis, acute interstitial nephritis, toxic nephropathies, and hemolytic uremic syndrome.

Clinical Findings

A. Symptoms and Signs

Usually the history shows some salient data such as sore throat or upper respiratory infection, diarrheal illness, use of antibiotics, or intravenous use of drugs (often illicit types). Bilateral back pain, at times severe, is occasionally noted. Gross hematuria may be present. It is unusual for pyelonephritis to present as acute kidney injury unless there is associated sepsis, obstruction, or involvement of a solitary kidney. Systemic diseases in which acute kidney injury occurs include Henoch–Schönlein purpura, systemic lupus erythematosus, and scleroderma. Human immunodeficiency virus (HIV) infection may present with acute kidney injury from HIV-associated nephropathy.

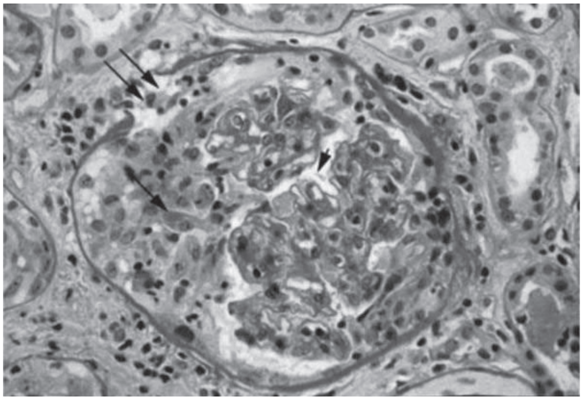
B. Laboratory Findings

1. Urine—Urinalysis discloses variably active sediments: many red or white cells and multiple types of cellular and granular casts. Phase contrast microscopy usually reveals dysmorphic red cells in the urine. In allergic interstitial nephritis, eosinophils may be noted. The urine sodium concentration may range from 10 to 40 mEq/L.

2. Blood test—Components of serum complement are often diminished (due to activation and consumption). In a few conditions, circulating immune complexes can be identified. Serologic tests may disclose systemic diseases such as lupus erythematosus (eg, antineutrophil antibody, anti-double-stranded DNA antibodies, anti-Smith antibodies). Thrombocytopenia and altered red cell morphologic structure are noted in peripheral blood smears in the hemolytic uremic syndrome. Rapidly progressive glomerulonephritis can be evaluated with tests for ANCAs (antineutrophil cytoplasmic antibodies) and anti-GBM titers (antiglomerular basement membrane antibodies).

3. Renal biopsy—Light microscopic examination shows characteristic changes of glomerulonephritis (ie, crescents within Bowman's capsule; see Figure 34–1), acute interstitial nephritis, or glomerular capillary thrombi (in hemolytic uremic syndrome). Immunofluorescence microscopy showing immune deposits helps confirm the diagnosis of rapidly progressive glomerulonephritis. The immune deposits can

Rapidly progressive glomerulonephritis



▲ **Figure 34–1.** High-power light micrograph showing an active hypercellular crescent containing fibrin, which has a bright red appearance (*long arrow*). Note that the severe inflammatory injury has led to fragmentation of the glomerular tuft (*short arrow*) and to creation of a rent in the capsule (*double arrow*). (Used with permission from Helmut Rennke, MD.)

be further divided into subendothelial (lupus nephritis), subepithelial (postinfectious glomerulonephritis), or mesangial (IgA nephropathy).

C. X-Ray Findings

Dye studies should be avoided because of the risk of contrast-induced renal injury. For this reason, sonography is preferable to rule out obstruction.

Treatment

Therapy is directed toward removing the underlying injurious constituent, for example, eradication of infection, removal of antigen, elimination of toxic materials and drugs, suppression of autoimmune mechanisms, removal of autoimmune antibodies, or a reduction in effector-inflammatory responses. Immunotherapy may involve drugs (corticosteroids) or the temporary use of plasmapheresis. Initiation of supportive dialysis may be required (see discussion following below).

Nonspecific intrarenal causes of acute kidney injury include acute tubular necrosis and acute cortical necrosis. The latter is associated with intrarenal intravascular coagulation and has a poorer prognosis than the former. These forms of acute kidney injury usually occur in hospital settings. Various morbid conditions leading to septic syndrome-like physiologic disturbances are often present.

Degenerative changes of the distal tubules (lower nephron nephrosis) are believed to be due to ischemia. With dialysis, most of these patients recover—usually completely—provided intrarenal intravascular coagulation and cortical necrosis does not occur.

Elderly patients, who are more vulnerable to this form of oliguric acute kidney injury, develop following hypotensive episodes. It appears that exposure to some drugs such as nonsteroidal anti-inflammatory agents may increase the risk of acute tubular necrosis. Although the classic picture of lower nephron nephrosis may not develop, a similar nonspecific acute kidney injury is noted in some cases of mercury (especially mercuric chloride) poisoning and following exposure to radiocontrast agents, especially in patients with preexisting renal impairment, diabetes mellitus, or myeloma.

Clinical Findings

A. Symptoms and Signs

Usually the clinical picture is that of the associated clinical state. Dehydration and shock may be present concurrently, but the urine output and acute kidney injury fail to improve following administration of intravenous fluids, in contrast to patients who have prerenal renal failure (see preceding discussion). On the other hand, there may be signs of excessive fluid retention in patients with acute kidney injury following radiocontrast exposure. Symptoms of uremia per se (eg, altered mentation or gastrointestinal symptoms) are unusual in acute kidney injury (in contrast to chronic kidney disease).

B. Laboratory Findings (Table 34–2)

1. Urine—The specific gravity is usually low or fixed in the 1.005–1.015 range. Urine osmolality is also low (<450 mOsm/kg and U:P osmolal ratio < 1.5:1 [where U:P = urine osmolality: plasma osmolality ratio]). Urinalysis often discloses tubular cells and granular casts; the urine may be muddy brown. If the urine is heme-positive, but no red cells are seen on microscopy, one must be concerned about the presence of pigment nephropathy (myoglobinuria or hemoglobinuria). Tests for differentiating myoglobin pigment are available.

2. Central venous pressure—This is usually normal to slightly elevated.

3. Fluid challenges—There is no increase in urine volume following intravenous administration of mannitol or physiologic saline. Occasionally, following the use of furosemide or "renal doses" of dopamine (1–5 μg/kg per minute), a low urine output is converted to a high fixed urine output. However, traditionally, it was believed that by converting patients with oliguric AKI into nonoliguric states by the technique described above translates into a better prognosis, this does not appear to be evidence-based. In fact, recent studies seem to suggest worse outcomes in those administered loop diuretics during or in response to an AKI.

Treatment

If there is no response to the initial fluid or mannitol challenge, the volume of administered fluid must be sharply curtailed to noted losses. An assessment of serum creatinine and BUN and of the concentrations of electrolytes is necessary to predict the possible use of dialysis. With appropriate regulation of the volume of fluid administered, maintenance of nutritional intake to provide a caloric content of 30–35 kcal/kg is used to correct or reduce the severity of the catabolic state accompanying acute tubular necrosis.

Serum potassium must be closely monitored to ensure early recognition of hyperkalemia. This condition can be treated with (1) intravenous sodium bicarbonate administration; (2) Kayexalate, 25–50 g (with sorbitol) orally (enema preparations are less favored because of the risk of bowel ischemia); (3) intravenous glucose and insulin; and (4) intravenous calcium preparations to prevent cardiac irritability (usually given with electrocardiographic changes, eg, peaked T waves, widening of QRS complexes).

Strategies to prevent the development of contrast-induced nephropathy include administration of normal saline and sodium bicarbonate infusions, *N*-acetylcysteine administration, and preemptive hemodialysis and hemodiafiltration. None has been definitively shown in randomized trials to confer protective effects, except for maybe volume expansion. The use of low-osmolar contrast dye has been adopted as standard, although no added benefits can be shown with iso-osmolar (iodixanol) contrast material.

Peritoneal dialysis or hemodialysis should be used as necessary to avoid or correct uremia, hyperkalemia, or fluid overload. Hemodialysis in patients with AKI can be either be intermittent or continuous (with arteriovenous or venovenous hemofiltration techniques). Vascular access is obtained with percutaneous catheters. The continuous dialysis techniques allow for easier management in many hemodynamically unstable patients in intensive care units.

There remains no consensus over what the best modality of renal replacement therapy is among patients with AKI. Continuous venovenous hemofiltration/hemodialysis/hemodiafiltration did not confer a more favorable survival or renal recovery benefit compared with intermittent forms of dialysis. Earlier reports of more intensive dialysis prescriptions in AKI (6 days per week vs every-other-day dialysis) showing superior survival are not substantiated by more recent evidence. What has emerged, however, is the need for meticulous attention to the delivered dialysis dose with each session and to minimize interruptions in dialytic therapy because of poor vascular access.

▶ Prognosis

Most cases are reversible within 7–14 days. Residual renal damage may be noted, particularly in elderly patients.

POSTRENAL AKI

The conditions listed in Table 34–1 involve primarily the need for urologic diagnostic and therapeutic interventions. Following lower abdominal surgery, urethral or ureteral obstruction should be considered as a cause of AKI. The causes of bilateral ureteral obstruction are (1) peritoneal or retroperitoneal neoplastic involvement, with masses or nodes; (2) retroperitoneal fibrosis; (3) renal calculi; and (4) postsurgical or traumatic interruption. With a solitary kidney, ureteral stones can produce total urinary tract obstruction and acute kidney injury. Urethral or bladder neck obstruction is a frequent cause of renal failure, especially in elderly men (prostatic enlargement). Posttraumatic urethral tears are discussed in Chapter 18.

▶ Clinical Findings

A. Symptoms and Signs

Pain and tenderness over the costovertebral angle often are present. If there has been an operative ureteral injury with associated urine extravasation, urine may leak through a wound. Edema from overhydration may be noted. Ileus is often present along with associated abdominal distention and vomiting.

B. Laboratory Findings

Urinalysis rarely is helpful. A large volume of urine obtained by catheterization may be both diagnostic and therapeutic for lower tract obstruction.

C. X-Ray Findings

Radionuclide renal scans may show a urine leak or, in cases of obstruction, retention of the isotope in the renal pelvis. Ultrasound examination often reveals a dilated upper collecting system with deformities characteristic of hydronephrosis.

D. Instrumental Examination

Cystoscopy and retrograde ureteral catheterization demonstrate ureteral obstruction.

▶ Treatment

For further discussion of ureteral injuries, see Chapter 18.

BIBLIOGRAPHY

Anonymous: Intensive care nephrology. J Am Soc Nephrol 2001;12(Suppl 17):S1.

Bellomo R et al: Acute dialysis quality initiative workup: Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–R212.

Forni LG, Hilton PJ: Continuous hemofiltration in the treatment of acute renal failure. New Engl J Med 1997;336:1303.

Fredrich JO et al: Meta-analysis: Low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005;142(7):510–524.

Gines P, Arroyo V: Hepatorenal syndrome. J Am Soc Nephrol 1999;10:1833.

Gonzales DA et al: A meta-analysis of N-acetylcysteine in contrast-induced nephrotoxicity: Unsupervised clustering to resolve heterogeneity. BMC Med 2007;5:32.

Lassnigg A et al: Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 2000;11(1):97–104.

Marik PE et al: Low-dose dopamine does not prevent acute renal failure in patients with septic shock and oliguria. Am J Med 1999;107:387.

Merten GJ et al: Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. JAMA 2004;291:2328–2334.

Murphy SW et al: Contrast nephropathy. J Am Soc Nephrol 2000;11:177.

Nolan CR, Anderson RJ: Hospital-acquired acute renal failure. J Am Soc Nephrol 1998;9:710.

Palevsky PM et al: Intensity of renal support in critically ill patients with acute kidney injury. New Engl J Med 2008;359:7–20.

Pannu N et al: Renal replacement therapy in patients with acute renal failure: A systematic review. JAMA 2008;299:793–805.

Schiffl H et al: Daily hemodialysis and the outcome of acute renal failure. New Engl J Med 2002;346:305.

Schor N: Acute renal failure and the sepsis syndrome. Kidney Int 2002;61:764.

Star RA: Treatment of acute renal failure. Kidney Int 1998;54:1817.

Tepel M et al: Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. New Engl J Med 2000;343:180.

This page intentionally left blank

Chronic Kidney Disease and Renal Replacement Therapy

35

Brian K. Lee, MD; & Flavio G. Vincenti, MD

OVERVIEW

In chronic kidney disease (CKD), reduced clearance of certain solutes principally excreted by the kidney results in their retention in the body fluids. The solutes are end products of endogenous metabolism as well as exogenous substances (eg, drugs). The most commonly measured indicators of renal failure are blood urea nitrogen (BUN) and serum creatinine. The renal clearance of creatinine (as calculated from a 24-hour urine collection) is often used as a surrogate measure of glomerular filtration rate (GFR).

Renal failure may be classified as acute or chronic depending on the rapidity of onset and the subsequent course of azotemia. An analysis of the acute or chronic development of renal failure is important in understanding physiologic adaptations, disease mechanisms, and ultimate therapy. In individual cases, it is often difficult to establish the duration of renal failure. Historical clues such as preceding hypertension or radiologic findings such as small, shrunken kidneys tend to indicate a more chronic process. Acute kidney injury (AKI) may progress to irreversible chronic renal failure. For a discussion of AKI, see Chapter 34.

A new classification has been established by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (K/DOQI). This delineates CKD by varying degrees of reduced GFR, either in the presence or absence of structural or functional renal abnormalities (available on the NFK website: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p4_class_g1.htm). This has been useful in studies of the progression of CKD, especially in varying drug regimens to reduce the rate of worsening of GFRs.

There are now numerous online calculators that can estimate a person's GFR (eGFR) on the basis of the creatinine value, one example of which is available through the National Kidney Foundation (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). Although not perfect, these calculations help us to alert patients with subtle renal function impairment in the face of creatinine values within the normal reference ranges.

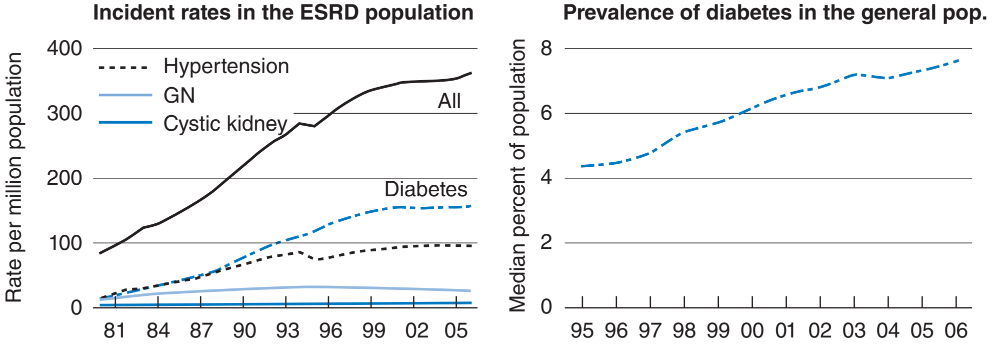
The incidence of end-stage renal disease (ESRD) reached 378 cases per million population in 2015, after a period of relative stability between 2001 and 2005. This increase can be explained almost entirely by the uptake in incidence of diabetic nephropathy over the same period (Figure 35–1). Particularly affected are older patients (75+ years old) and African-Americans (3.6 times higher than Caucasians; Figures 35–2 and 35–3). The severity and the rapidity of development of uremia are difficult to predict. The use of dialysis and transplantation is expanding rapidly worldwide. As of December 31, 2015, more than 440,000 prevalent ESRD patients in the United States were treated with hemodialysis, with around 49,000 patients treated with peritoneal dialysis. There are approximately 208,000 patients with a functioning kidney transplant.

Historical Background

There are various causes of progressive renal dysfunction leading to end-stage or terminal renal failure. In the 1800s, Bright described several dying patients who presented with edema, hematuria, and proteinuria. Chemical analyses of sera drew attention to retained nitrogenous compounds and an association was made between this and the clinical findings of uremia. Although the pathologic state of uremia was well described, long-term survival was not achieved until chronic renal dialysis and renal transplantation became available after 1960–1970. Significant improvements in patient survival have been made in the past 50 years.

Etiology

A variety of disorders are associated with CKD. Either a primary renal process (eg, glomerulonephritis, pyelonephritis, congenital hypoplasia) or a secondary one (owing to a systemic process such as diabetes mellitus or lupus erythematosus) may be responsible. It is now believed that once there is kidney injury, the initially adaptive hyperfiltration to undamaged



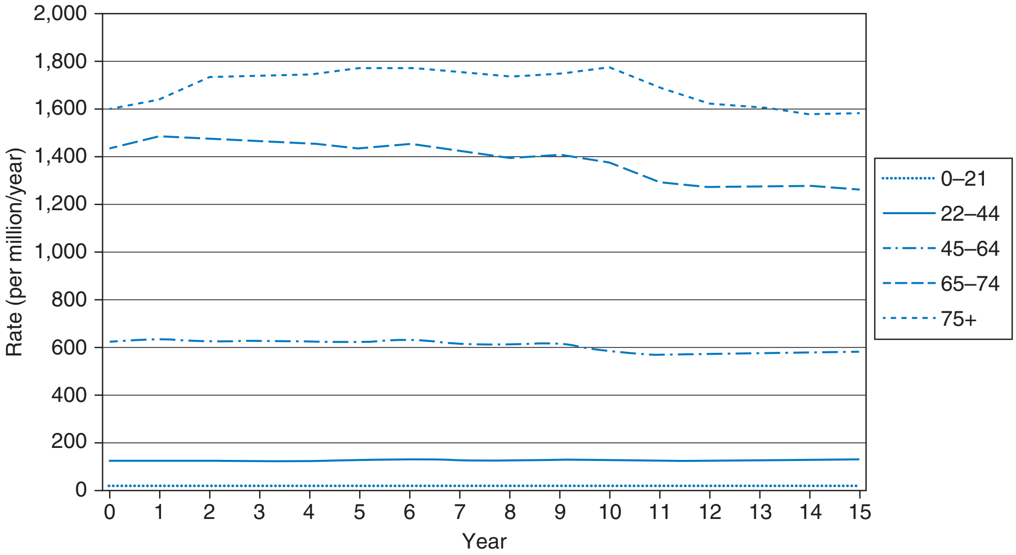
▲ **Figure 35–1.** Incident ESRD patients; rates adjusted for age, gender, and race. (Data from Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System.)

nephron units produces further stress and injury to remnant kidney tissue, ultimately leading to worsening renal function and urinary abnormalities (ie, proteinuria). The patient will show progression from one stage of CKD severity to the next. Superimposed physiologic alterations secondary to dehydration, infection, obstructive uropathy, or hypertension may put a borderline patient into uncompensated chronic uremia.

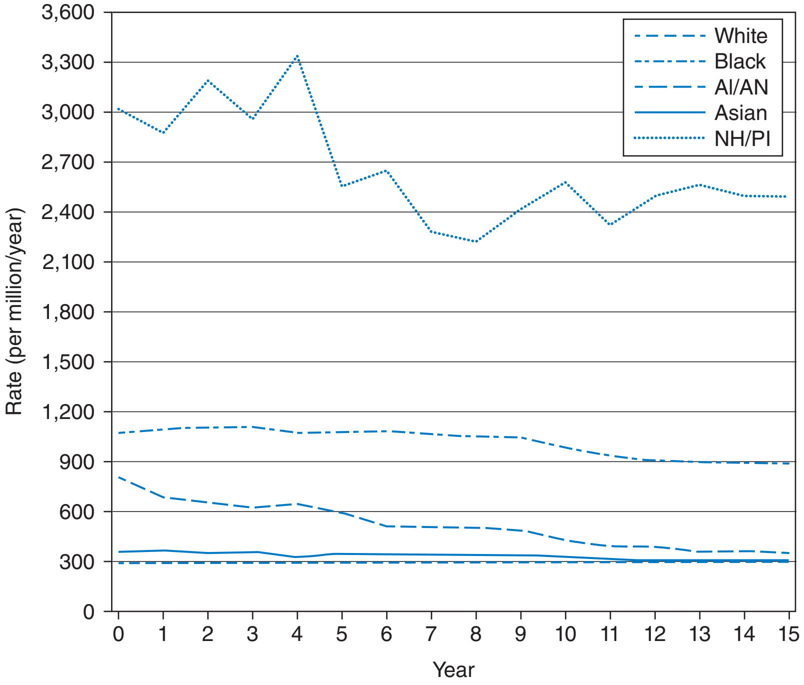
Clinical Findings

A. Symptoms and Signs

With milder CKD, there may be no clinical symptoms. Symptoms such as pruritus, generalized malaise, lassitude, forgetfulness, loss of libido, nausea, and easy fatigability are frequent and nonfocal complaints in moderate to severe CKD. Growth failure is a primary complaint in preadolescent patients. Symptoms of a multisystem disorder (eg, systemic lupus erythematosus) may be present coincidentally. Most patients with CKD have elevated blood pressure secondary to volume overload or from hyperreninemia. However, the blood pressure may be normal or low if patients have marked renal salt-losing tendencies (eg, medullary cystic disease). The pulse and respiratory rates are rapid as manifestations of anemia and metabolic acidosis. Clinical findings of uremic fetor, pericarditis, neurologic findings of asterixis, altered mentation, and peripheral neuropathy are present only with



▲ **Figure 35–2.** Trends in adjusted ESRD incidence rate, by age group, in the US population, 2000–2015. Standardized for sex and race. The standard population was the US population in 2011. (Reproduced with permission from the United States Renal Data System. End-stage Renal Disease (ESRD) in the United States, 2017.)



▲ **Figure 35–3.** Trends in adjusted ESRD incidence rate, by race, in the US population, 2000–2015. The standard population was the US population in 2011. (Reproduced with permission from the United States Renal Data System. End-stage Renal Disease (ESRD) in the United States, 2017.)

severe, stage V CKD. Palpable kidneys suggest polycystic disease. Ophthalmoscopic examination may show hypertensive or diabetic retinopathy. Alterations involving the cornea/lens have been associated with metabolic disease (eg, Fabry disease, cystinosis, Alport hereditary nephritis).

B. History

In 20% of cases, there is a family history of CKD. A report of antecedent nephritis episodes or a history of previous proteinuria may be elicited. It is important to review drug usage and possible toxic exposures (eg, lead).

C. Laboratory Findings

1. Urine composition—The urine volume varies depending on the type of renal disease. Quantitatively normal amounts of water and salt losses in urine can be associated with polycystic and interstitial forms of disease. Usually, however, urine volumes are quite low when the GFR falls below 5% of normal. The urinary concentrating (fixed, low-value specific gravity) and acidification (high urinary pH) mechanisms may be impaired. Daily salt losses become less regulated, and, if they are low, a state of positive sodium balance results in edema. Proteinuria can be variable. Urinalysis examinations may reveal mononuclear white blood cells (leukocyturia) and occasionally broad waxy casts, but usually the urinalysis is nonspecific and inactive.

2. Blood testing—Often seen is a picture of normocytic, normochromic anemia, the so-called anemia of chronic disease. With worsening renal function, iron deficiency may ensue. Despite normal platelet counts, patients suffer from dysfunction (thrombasthenia), characterized by abnormal bleeding times.

Several abnormalities in serum electrolytes and mineral metabolism become manifest when the GFR drops below 30 mL/min (in the case of secondary hyperparathyroidism, impairment may begin with GFR < 60 mL/min). Progressive reduction of body buffer stores and an inability to excrete titratable acids result in progressive metabolic acidosis characterized by reduced serum bicarbonate and compensatory respiratory hyperventilation. The metabolic acidosis of uremia is associated with a normal anion gap, hyperchloremia, and normokalemia. However, as renal dysfunction progresses, some patients may develop an anion gap acidosis (due to the buildup of organic anions). Hyperkalemia is rarely seen unless the GFR is below 5 mL/min. In patients with interstitial renal diseases, gouty nephropathy, or diabetic nephropathy, hyperchloremic metabolic acidosis with hyperkalemia (renal tubular acidosis, type IV) may develop. In these cases, the acidosis and hyperkalemia are out of proportion to the degree of renal failure and are related to a decrease in renin and aldosterone secretion. In moderate to severe CKD, multiple factors lead to an increase in serum phosphate and a decrease in serum calcium. The hyperphosphatemia develops as a consequence of reduced phosphate clearance by the kidney. In addition, vitamin D activity is diminished because of reduced conversion of 25-OH vitamin D to the active form, 1,25-OH vitamin D in the kidney by the enzyme 1α-hydroxylase. These alterations lead to secondary hyperparathyroidism with skeletal changes of both osteomalacia and osteitis fibrosa cystica. Uric acid levels are frequently elevated but rarely lead to calculi or gout during chronic uremia.

D. X-Ray Findings

Patients with reduced renal function should not be routinely subjected to radiographic studies involving iodinated contrast (nephrotoxic). Renal sonograms are helpful in determining renal size (usually small) and cortical thickness (usually thin) and in localizing tissue for percutaneous renal biopsy. Bone x-rays may show retarded growth, osteomalacia (renal rickets), or osteitis fibrosa (brown tumors). Soft-tissue or vascular calcification may be noted on plain films. Patients with polycystic kidney disease will have variably large kidneys with evident cysts (on sonograms or abdominal CT scans).

E. Renal Biopsy

Renal biopsies may not reveal much except nonspecific interstitial fibrosis and glomerulosclerosis. There may be pronounced vascular changes consisting of thickening of the media, fragmentation of elastic fibers, and intimal proliferation, which may be secondary to uremic hypertension or due to primary arteriolar nephrosclerosis. Percutaneous biopsies of end-stage shrunken kidneys may be complicated by bleeding (due to the uremic platelet dysfunction; see section titled "Blood Testing"). The bleeding tendency can be ameliorated once the patient starts on dialysis, or with the use of desmopressin (mediates release of endothelial stores of factor VIII–von Willebrand factor multimers).

▶ Treatment

Recent studies indicate some benefit of drugs to reduce progression of CKD. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers in slowing down renal decline has been well documented, especially in the diabetic population with significant proteinuria. With the addition of aldosterone antagonists to optimize blood pressure control, patients need to be followed closely for potential hyperkalemia. Lipid-lowering agents should be employed to lower the already accelerated risk of atherosclerotic disease in the ESRD population and can potentially retard the progression of renal dysfunction.

Overall, management should be conservative until it becomes impossible for patients to continue their customary lifestyles. Restriction of dietary protein (0.8–1.0 g/kg daily), potassium, and phosphorus is recommended. Additionally, maintenance of close sodium balance in the diet is necessary so that patients become neither sodium expanded nor depleted. This is best done by the accurate and frequent monitoring of the patient's weight. Use of oral bicarbonate (0.5–1 mEq/kg daily) can be helpful when moderate acidemia occurs (aim for serum HCO_3 level ≥ 23 mEq/L). Anemia can be treated with recombinant erythropoietin given subcutaneously (aiming for hemoglobin levels between 11.0 and 12.0 g/dL per the K/DOQI guidelines). Prevention of possible uremic osteodystrophy and secondary hyperparathyroidism requires close attention to calcium and phosphorus balance. Phosphate-retaining antacids and calcium or vitamin D supplements may be needed to maintain the balance. Cinacalcet can directly reduce parathyroid hormone secretion. If severe secondary hyperparathyroidism occurs, subtotal parathyroidectomy may be needed.

A. Chronic Peritoneal Dialysis

Chronic peritoneal dialysis is used electively or when circumstances (ie, no available vascular access) prohibit chronic hemodialysis. Ten percent of dialysis is done with this treatment. Improved soft catheters can be used for repetitive peritoneal lavages. In comparison to hemodialysis, small molecules (eg, creatinine and urea) are cleared less effectively than larger molecules, but excellent treatment can be accomplished. Intermittent thrice-weekly treatment (IPPD), continuous cycler-assisted peritoneal dialysis (CCPD), or chronic ambulatory peritoneal dialysis (CAPD) is possible. With the latter, the patient performs three to five daily exchanges using 1–2 L of dialysate at each exchange. The dialysate contains a high glucose concentration and the peritoneal surface serves as the semipermeable membrane. Bacterial contamination and peritonitis are becoming less common with improvements in connection technology. Over time, many patients will transition to hemodialysis due to either peritoneal membrane failure (eg, peritoneal sclerosis, adhesions) or inadequate dialysis as native renal clearance of solutes deteriorates.

B. Chronic Hemodialysis

Chronic hemodialysis using semipermeable dialysis membranes is now widely performed. Access to the vascular system is provided by an arteriovenous fistula, vascular grafts (with autologous saphenous vein or synthetic material), or a percutaneous permcatheter (placed either surgically or with interventional radiology). Most dialyzer membranes nowadays are made with biocompatible materials (fewer blood–membrane reactions). Body solutes and excessive body fluids can be easily cleared by using dialysate fluids of known chemical composition. Newer, high-efficiency membranes (and high-flux) are serving to reduce dialysis treatment time.

Treatment is intermittent—usually 3–5 hours thrice weekly. Computer modeling, using measurements of urea kinetics, has provided more precise hemodialysis prescriptions. Treatments may be given in a kidney center, a satellite unit, or the home. Home dialysis is optimal because it provides greater scheduling flexibility and is generally more comfortable and convenient for the patient, but only 20% of dialysis patients meet the requirements for this type of therapy. There is rising interest in this modality of treatment given better patient survival and quality of life.

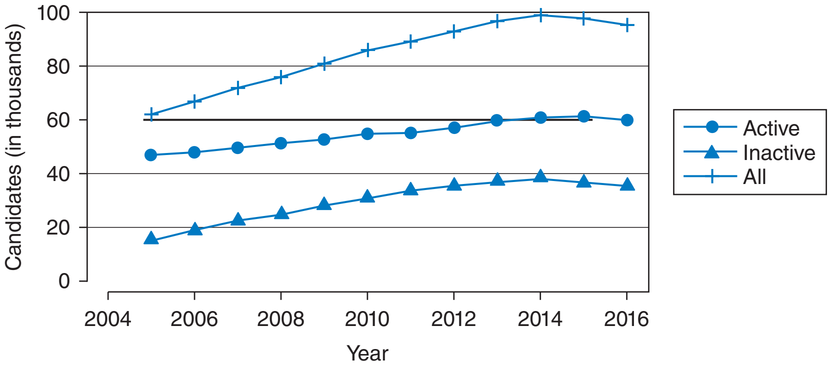
More widespread use of dialytic techniques has permitted greater patient mobility. Treatment on vacations and business trips can be provided by prior arrangement. There are even dedicated cruise ships that provide dialysis.

Common problems with either type of chronic dialysis include infection, bone symptoms, technical accidents, persistent anemia, and psychological disorders. The excessive morbidity and mortality associated with atherosclerosis often occurs with long-term treatment. It is now recognized that occasionally uremic patients, despite dialysis, can develop wasting syndrome, cardiomyopathy, polyneuropathy, and secondary dialysis-amyloidosis so that kidney transplant must be urgently done. Routine bilateral nephrectomy should be avoided because it increases the transfusion requirements of dialysis patients. Nephrectomy in dialysis patients should be reserved for cases of refractory hypertension, reflux with infection, and cystic disease with recurrent bleeding and pain. The dialysis patient can occasionally have acquired renal-cystic disease. Such patients need close monitoring for the development of in situ renal cell carcinoma.

Yearly costs range from an average of $50,000 for a patient who receives dialysis at home to as much as $50,000–$75,000 for a patient treated at dialysis centers (with those dialyzing through an AV graft or catheter incurring more cost), but much of this is absorbed under HR-1 (Medicare) legislation. If the patient has no other systemic problems (eg, diabetes), the mortality rate is 8–10%/year once maintenance dialysis therapy is instituted. Despite these medical, psychological, social, and financial difficulties, most patients lead productive lives while receiving dialysis treatment.

C. Renal Transplantation

After immunosuppression techniques and genetic matching were developed, renal allotransplantation became an acceptable alternative to maintenance hemodialysis. Improved short-term transplant results are now noted owing to the development of newer immunosuppressant drugs. Currently employed posttransplant drugs include prednisone, mycophenolate mofetil (and its enteric-coated formulation), cyclosporine, tacrolimus, and sirolimus/everolimus. There are numerous novel medications under investigation that inhibit different pathways in the allorecognition mechanism, including a variety of injectable bioagents. The major advantage of transplantation is reestablishment of nearly normal and constant body physiology and chemistry. Diet can be less restrictive. The disadvantages include bone marrow suppression, susceptibility to infection, oncogenesis risks, and the psychological uncertainty of the allograft's future. Most of the disadvantages of transplantation are related to the medicines given to counteract the rejection. Later problems with transplantation include recurrent disease in the transplanted kidney and an increased incidence of cancer. Genitourinary infection appears to be of minor importance if structural urologic complications (eg, leaks) do not occur. However, the shortage of organ supply continues to plague the transplant community. As of 2016, there were roughly 100,000 patients on the kidney transplant waiting list, with annual death rates of 65 patients/1000 patient-years at risk (Figure 35–4).



▲ **Figure 35–4.** Adults listed for kidney transplants on December 31 of each year. Candidates concurrently listed at multiple centers are counted once. Those with concurrent listings and active at any program are considered active. Includes kidney and kidney-pancreas listings. (Reproduced with permission from Hart A, Smith JM, Skeans MA, et al: OPTN/SRTR 2016 Annual Data Report: Kidney, Am J Transplant. 2018 Jan;18 Suppl 1:18–113.)

Nephrology centers, with close cooperation between medical and surgical staff, attempt to use these treatment alternatives of dialysis and transplantation in an integrated fashion.

For a more detailed review, see Chapter 35.

BIBLIOGRAPHY

Anonymous: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification (excerpts). Am J Kidney Dis 2002;39(Suppl 1):1.

Anonymous: Clinical Practice Guidelines and Clinical Practice Recommendations 2006: K/DOQI Advisory Panel (excerpts). Am J Kidney Dis 2006;48(Suppl 1):1.

Anonymous: 2008 OPTN/SRTR Annual Report 1998–2007. HHS/HRSA/HSB/DOT; UNOS; Arbor Research Collaborative for Health.

Astor BC et al: Type of vascular access and survival among incident hemodialysis patients. J Am Soc Nephrol 2005;16:1449.

Atkins RC et al: Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 2005;45:281.

Coresh J et al: Chronic kidney disease awareness, prevalence and trends among U.S. adults. J Am Soc Nephrol 2005;16:180.

Daugas E et al: HAART-related nephropathies in HIV-infected patients. Kidney Int 2005;67:393.

El Nahas M: The global challenge of chronic kidney disease. Kidney Int 2005;68:2918.

Go AS et al: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. New Engl J Med 2004;351:1296.

Hsu CY et al: Elevated blood pressure and risk of end-stage renal disease in subjects without kidney disease. Arch Int Med 2005; 165:923.

Levey AS et al: A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.

Muntner P et al: Association of serum intact parathyroid hormone with lower estimated glomerular filtration rate. Clin J Am Soc Nephrol 2009;4:186–194.

Remuzzi G et al: Chronic renal disease: Renoprotection benefits of renin-angiotensin system inhibition. Ann Intern Med 2002; 136:304.

Stewart JH et al: Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease. J Am Soc Nephrol 2003; 14:197.

US Renal Data Systems: 2008–2009 Annual Data Report. (Available online at: http://www.usrds.org/adr.htm; accessed 7/6/10).

Woods JD et al: Comparison of mortality with home hemodialysis and center hemodialysis: A national study. Kidney Int 1996;49(5): 1464–1470.

Renal Transplantation

36

John M. Barry, MD

RENAL TRANSPLANTATION: INTRODUCTION

The purpose of this chapter is to provide the general urologist and the urologist-in-training with an overview of renal transplantation. It is meant to be practical.

The incidence of end-stage renal disease (ESRD) in the United States is approximately 380 per million population per year, and it increases with age (United States Renal Data System, 2017). One-half of ESRD patients in the United States are over 65 years old. Diabetes mellitus, glomerulonephritis, hypertension, and cystic kidney diseases are, in descending order, the four main causes of ESRD. Patients treated with renal replacement therapy have decreased life expectancies when compared with the general population, and the annual mortality from ESRD is greater than that for either breast or prostate cancer (United States Renal Data System, 2017; Seigel et al, 2018). When dialysis and transplantation are compared, better patient survival, quality of life, and healthcare cost savings are reported for kidney transplant recipients (Wolfe et al, 1999; Grams et al, 2010). There are about 90,000 dialysis patients awaiting kidney transplantation, half of whom are on the active waiting list, a list that remains nearly three times larger than the supply of donor kidneys (United States Renal Data System, 2017).

Two-thirds of the nearly 20,000 kidneys transplanted in the United States each year are from deceased donors, and a quality-matched deceased donor kidney allocation system has been implemented to decrease unrealized life-years of recipients, reduce wastage of marginal kidneys, and decrease access disparities. A Kidney Donor Profile Index (KDPI) based on 10 donor factors (age, height, weight, ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, hepatitis C status, and donation after cardiac death status) was developed to replace the binary categories of standard criteria (SCD) and extended criteria donors (ECD) that incorporated only four factors (United States Renal Data System, 2017). A deceased donor with a KDPI of 85% is about the same as an ECD. An expected posttransplant survival (EPTS) score is developed for kidney transplant candidates. The EPTS is based on age, time on dialysis, prior transplantation of any organ, and the presence of diabetes. Low scores are good scores, and there is preferential allocation of donor kidneys with EPTS scores of 20% or less to candidates with EPTS scores of 20% or less. KDPI and EPTS calculators can be found at optn.transplant.hsra.gov/resources/allocation-calculators.

The rates for 10-year deceased donor kidney transplant graft and patient survivals are 48% and 64%, respectively. The 10-year living donor kidney graft and patient survivals are 62% and 78%, respectively (United States Renal Data System, 2017).

For decades, kidney transplantation has provided examples of (1) a multidisciplinary approach to complex, expensive patient care; (2) the advantages of a mandatory national registry; (3) the use of antibody therapy; and (4) the rewards and frustrations of dealing with a complex national healthcare system with a major single payer and multiple private healthcare insurers and agencies.

KIDNEY TRANSPLANT CANDIDATE EVALUATION

Table 36–1 shows the questions that need to be answered by the multidisciplinary kidney transplant evaluation.

A. ESRD Recurrence

Examples of causes of ESRD that may result in kidney transplant loss due to recurrence of disease are primary oxalosis, cystinosis, atypical hemolytic uremic syndrome (aHUS), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, IgA nephropathy, systemic lupus erythematosis, anti-glomerular basement membrane disease, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, renal amyloidosis,

Table 36–1. Questions addressed by multidisciplinary evaluation of a transplant candidate.

What is the cause of ESRD and the risk of recurrence in a kidney transplant?
What psychosocial or financial problems could prevent compliance with posttransplant care?
Is active, invasive infection present?
Is active malignancy present?
Are there anatomic or functional barriers to technical success?
What are the immunologic risk factors?
What would be the transplant candidate's survival without ESRD?
Is there a potential living renal donor?

and Fabry disease. Oxalosis is often treated with combined liver and kidney transplantation. Examples of diseases that do not recur in a kidney transplant are the polycystic renal diseases, renal dysplasia, and chronic pyelonephritis. Transplant nephrologists provide this information.

B. Psychosocial or Financial Problems

Noncompliance with a complex posttransplant regimen is a preventable cause of kidney graft loss, and psychosocial and financial assessments are performed to identify and correct problems that could result in noncompliance. Teenage years, lack of funds to pay for maintenance immunosuppression, mental dysfunction, or an inadequate support system are examples of factors that can lead to kidney graft loss. Pretransplant nurse coordinators, pharmacy, social service and financial services provide this information.

C. Active Infection

The current CDC immunization recommendations are followed (Centers for Disease Control and Prevention, 2018). Meningococcal vaccination is advised for asplenic patients and patients who may receive the complement inhibitor, eculizumab, which is used to prevent or treat the thrombotic microangiopathy of aHUS. Hepatitis C can be treated before transplantation. The most common sites of existing infection in the potential renal transplant recipient are the chest and urinary tract. Screening for pulmonary infectious diseases is with chest x-ray and tuberculosis test. Patients with inactive tuberculosis usually receive months of prophylactic isoniazid. This need not delay transplantation because the treatment course can be continued after transplantation.

Urinary tract infection must be resolved or controlled prior to transplantation. Patients with symptomatic, recent, or recurrent urinary tract infections may require surveillance urinalyses and urine cultures. Treatment is based on culture and sensitivity results. If renal infection, stones, or ureteral obstruction is a real or potential source of recurrent or chronic bacteriuria, nephrectomy is performed, usually 6–8 weeks prior to transplantation.

Prophylactic segmental colectomy may be necessary for patients with recurrent diverticulitis. Pretransplant cholecystectomy is not required for asymptomatic cholelithiasis. Dental infections must be resolved before immunosuppression.

Cytomegalovirus (CMV) antibody levels are determined because posttransplant CMV infection can result in significant morbidity and mortality. Some transplant programs do CMV donor–recipient matching to reduce the risk and expense of posttransplant CMV infection or prophylaxis when a CMV seronegative recipient receives a kidney from a CMV seropositive donor. If hepatitis B or C viral antibody levels indicate active hepatitis, these patients are excluded from transplantation until cleared by hepatology consultation because of the risk of hepatitis exacerbation with immunosuppression. Recipients who are human immunodeficiency virus (HIV)-positive may qualify for transplantation if CD4-lymphocyte counts are satisfactory (Yoon et al, 2011). Many centers obtain herpes simplex viral (HSV) titers. If the titers are elevated or the patient has a history of herpes virus infection, antiviral prophylaxis is commonly instituted for 3–4 months after transplantation. An infectious disease opinion is sought for problem cases.

D. Malignancy

Guidelines for cancer screening change from time to time and among medical specialty organizations. The American Cancer Society periodically publishes guideline reviews that are widely accepted (Smith et al, 2018). A history of aristolochic acid ingestion, a commonly used herb for weight loss, or prior cyclophosphamide treatment warrant screening for urothelial carcinoma. Patients with treated cancer must have a low probability of recurrence by nomogram after transplantation. See Table 36–2 for suggested disease-free waiting

Table 36–2. Suggested disease-free waiting times before active listing after treatment of genitourinary cancers.

Cancer	Stage/risk	Grade	Wait time with no recurrence or progression
Kidney	T1aN0M0	Any	None
	T1bN0M0	Fuhrman 1–2	None
	T1bN0M0	Fuhrman 3–4	2 years
	≥T2	Any	2 years
Prostate	Low		None
	Intermediate		None
	High risk		2 years
Urothelial	≤T1, focal	Low	None
	≤T1	High or CIS	2 years
	≥T2	Any	2–5 years

Table 36–3. Questions to be answered by urinary tract evaluation of a kidney transplant candidate.

Does the bladder or its substitute fill?
Does the bladder or its substitute empty?
Is the patient dry?
Is there a prosthetic reservoir to be avoided at the time of transplant?
Is there an artificial urinary sphincter to be opened at the time of transplant?
Is genitourinary cancer present?
Should the native kidneys come out?

times before transplantation or active wait-listing for a kidney transplant. When in doubt, confer with a genitourinary cancer specialist.

E. Unsuitable Anatomy for Technical Success

See Table 36–3 for the issues to be settled by evaluation of the urinary tract, and Table 36–4 for the basic evaluation. An accurate voiding history in the oligoanuric transplant candidate may be impossible to obtain, and one has to settle for what the patient remembered it to be. The urinalysis may be invalid because of oliguria, and a multiorganism urine culture result can be ignored unless an intestinal–vesical fistula is suspected. The potential recipient must have an adequate urinary reservoir that naturally empties or can be emptied by intermittent catheterization, or a urinary conduit. If the candidate has a continent reservoir, the kidney transplant will need to have an estimated glomerular filtration rate of >35 mL/min because of the reabsorption of urinary electrolytes by intestinal mucosa (Hautmann et al, 1999). An ultrasound of the postvoid bladder or continent bladder substitute will screen for urinary retention. Contrast studies of continent reservoirs or urinary conduits are commonly done to check for stones, reflux, or obstruction. Significant urethral stricture disease and benign prostatic obstruction (BPO) must be treated, or a management plan must be put in place prior to transplantation. If enucleation prostatectomy or transurethral incision of the prostate is done, it is reasonable to keep the denuded prostatic fossa open for several weeks until reepithelialization occurs to prevent prostatic stricture. When native urine volume is inadequate, intermittent catheterization or placement of a suprapubic cystostomy tube at the time of bladder outlet surgery will allow the patient to fill the bladder with sterile water and void. Ultrasonography to detect hydronephrosis, stones, or tumors is a minimum evaluation of the upper urinary tract.

Table 36–4. Basic urinary tract evaluation.

Step	Checklist
History	UTIs, voiding dysfunction, stones, surgeries, cancer, penile prosthesis, artificial urinary sphincter, sexual function, aristolochic acid, cyclophosphamide, schistosomiasis
Exam	Abdomen, genitalia, prostate if > 50
Imaging	Ultrasound of kidneys, ureters, post-void bladder
Lab	UA, UC, PSA in men >50 years old
Rarely	Voiding cystourethrogram, urodynamics

Table 36–5. Indications for pretransplant nephrectomies.

Hypertension uncontrolled with medication
Recurrent pyelonephritis
Renal calculi not removable by minimally invasive procedures
Significant proteinuria (consider angioembolization)
Persistent antiglomerular basement membrane antibodies
Solid tumors
Polycystic kidneys with recurrent pyelonephritis, recurrent bleeding, chronic pain, early satiety, or extension into true pelvis

Renal tumors occur with increased frequency in patients who have the acquired cystic disease of chronic renal failure (Kuroda et al, 2011), and preliminary nephrectomy is often done for solid tumors. See Table 36–5 for a summary of the generally accepted indications for native kidney removal in kidney transplant candidates. It is reasonable to do nephrectomy at the time of transplantation for T1a and Fuhrman grade 1 or 2 T1b renal cell carcinomas and for uninfected kidneys.

Symptoms and signs of peripheral vascular disease are sought to ensure that arterial revascularization of the kidney graft is possible and that an ipsilateral lower extremity or buttock steal syndrome will not result from the transplant. To select an appropriate arterial anastomosis target, Doppler flow studies, with or without noncontrast CT scans of pelvic vessels and the splenic artery, are helpful in patients with severe peripheral vascular disease, in or those who have undergone abdominal or pelvic vascular reconstructive procedures. Foot ulcers must be healed prior to transplantation.

F. Life Expectancy Calculation

A major cause of mortality in ESRD is heart disease, and a cardiac assessment that may include echocardiography, nuclear medicine perfusion studies, and coronary arteriography is done in at-risk transplant candidates. Life expectancy calculations based on Charlson comorbidities can guide the selection of suitable candidates for transplantation (see Table 36–6). Ten-year life expectancies for Charlson Comorbidity scores of 1, 3, 5, and 7 are 96%, 22%, 21%, and 2%, respectively (Charlson Comorbidity Index, 2018). For example, a 55-year-old woman with ESRD due to diabetes mellitus and a history of myocardial infarction, peripheral

Table 36–6. Charlson Comorbidity Score/Index.

Points	Comorbidity
1 for	Each decade of age beginning at 50 years
1 for each	Uncomplicated diabetes mellitus, mild liver disease, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, connective tissue disease, peptic ulcer disease
2 for each	Diabetes mellitus with end-organ damage; any leukemia, lymphoma, or localized solid tumor; moderate to severe chronic kidney disease, hemiplegia
3 for each	Moderate to severe liver disease
6 for each	6 points for metastatic solid tumor, AIDS

vascular disease, chronic obstructive pulmonary disease, and transient cerebral ischemia attacks would have an estimated 10-year survival of 0%. With cure of her ESRD by a kidney transplant, it would be 2%. Should she undergo transplantation? This is decided by the members of the multidisciplinary selection committee.

G. Immunologic Risk Factors

An immunosuppression protocol can often be assigned at the multidisciplinary transplant selection conference. Antibody induction therapy is usually based on immunologic risk factors identified during the multidisciplinary recipient evaluation. Kidney transplant recipient immunologic risk factors are African ancestry, high anti-human leukocyte antigen (HLA) antibody levels from prior blood or platelet transfusions or pregnancy, systemic lupus erythematosus, aHUS, ABO-incompatibility, and early rejection of a previous organ transplant. Older recipients are considered to have reduced immune competence.

A lymphocyte-depleting agent (alemtuzumab or rabbit antithymocyte globlulin) is generally used for patients at high immunologic risk. An interleukin-2 receptor antibody (daclizumab) or no antibody is common for low-immunologic-risk recipients. Eculizumab is used in patients with complement-mediated microangionephropathy as the cause of ESRD. Maintenance immunosuppression is usually with a purine antagonist (azathioprine or mycophenolate mofetil), a calcineurin inhibitor (tacrolimus or cyclosporine), and decreasing doses of a glucocorticoid (prednisone). Sirlolimus, a mammalian target of rapamycin (mTOR) inhibitor, is sometimes used in place of tacrolimus or cyclosporine to prevent calcineurin inhibitor nephrotoxicity. A disadvantage of mTOR inhibitors is impairment of wound healing.

H. Living Renal Donors

If a transplant candidate is acceptable for transplantation and has a potential living kidney donor, the potential donor is assessed after he or she calls the transplant program to volunteer.

LIVING VERSUS DECEASED RENAL DONORS

▶ Living Renal Donors

A. Assessment

Living renal donation is not without risk. The 90-day mortality rate is 3.1/10,000 laparoscopic donor nephrectomies, and the corresponding rate for laparoscopic nondonor nephrectomy is 260 in 10,000 (Segev et al, 2010). The lifetime risk of a kidney donor developing ESRD is 90 in 10,000 cases, and the lifetime ESRD risks for healthy nondonors, and unscreened nondonors have been reported to be 14 in 10,000 cases and 326 in 10,000 cases, respectively (Muzaale et al, 2014).

Clinical practice guidelines have been developed for the screening of living kidney donors to minimize harm to the donors, and there is general agreement that nephrologists should assess the medical suitability, surgeons should assess surgical risk, and mental health professionals should discuss the correlation between mental health and transplant candidate eligibility with the recipient (Lentine et al, 2017). Generally accepted criteria for exclusion of a living renal donor are as follows: under-age minor; apolipoprotein L1 variant in African ancestry donor candidate (Newell et al, 2017); renal function below normal for age; proteinuria >300 mg/day; microalbuminuria >30 mg/day; body mass index >35 kg/m^2; blood pressure >140/90 with or without treatment; diabetes mellitus; nephrolithiasis if multiple stones, bilateral stone disease or high recurrence probability because of metabolic condition or anatomic abnormality; malignancy with risk of transmission to the recipient; malignancy with a future need for nephrotoxic therapy; infection with risk of transmission resulting in recipient morbidity or death; coercion; mental illness; and lack of social support and coping mechanisms. Sometimes a kidney biopsy is necessary to sort out the cause of otherwise unexplained microscopic hematuria in a potential donor.

The goals of imaging in the renal donor candidate are to define renal vasculature, renal structure and volume, collecting system anatomy, and presence or absence of urolithiasis, all at minimal morbidity for the donor. Three-dimensional spiral CT with and without intravenous contrast satisfies all these requirements.

One of the principles of living renal donation is to leave the better kidney with the donor. In the case of a gravid woman who has two equivalent kidneys and wishes to have children, the right kidney is the preferred donor kidney by some teams because of the higher incidence of pyelonephritis and hydronephrosis of pregnancy in the right kidney (Monga 1998).

B. Technique

Although laparoscopic donor nephrectomy is the most common surgical approach, and the left kidney is favored by recipient surgeons because of its longer, less delicate vein, the donor nephrectomy technique depends on a donor surgeon's abilities, the recipient surgeon's preferences and abilities, availability of specialized instruments, and donor and recipient expectations.

▶ Deceased Renal Donors

The goals of deceased donor kidney retrieval are the following: no transmission of infection, no transmission of cancer, retrieval of transplantable organs, and removal of histocompatibility specimens, usually lymph nodes and spleen. Kidney retrieval is most often part of a multiorgan retrieval process, and is done thorough a total midline, sternal splitting incision with in situ flushing with an ice-cold preservation solution through the aorta with drainage through the IVC or right atrium (Barry and Conlin, 2012). During liver retrieval, the portal venous system is flushed for rapid core cooling. Adult-sized kidneys are separated at the back table, reflushed, packaged, and sent to the organ bank for continued cold storage, or in the case of donation after cardiac death (DCD), initiation of machine perfusion. Machine perfusion is also commonly used for kidneys of marginal quality. Kidneys from small pediatric donors are not separated, so that they can be transplanted en-bloc into one recipient.

RECIPIENT SELECTION

The donor and recipient must be ABO-compatible and have a negative donor–recipient lymphocytotoxic crossmatch. A national point system for selection of a deceased donor kidney transplant recipient is based on ABO blood group compatibility, histocompatibility, wait time, quality of kidney, previous living organ donor, and EPTS. Children are given preference. Because of preservation time limits, the matches are determined in order, for the best local, regional, and national recipients. When living donor–recipient pairs are found to be ABO- or crossmatch-incompatible, compatible donor–recipient pairs can be developed through kidney swap programs or donor–recipient chains.

At the time of admission for renal transplantation, a rapid workup is performed to detect intercurrent illness that could prevent a successful operative procedure and immunosuppression. Sometimes, a lymphocyte–toxicity crossmatch needs to be repeated because of recent blood transfusion or infection. If not done with the initial multidisciplinary recipient evaluation, some programs do a thrombophilia assessment at this time to detect a hypercoagulable state and plan an anticoagulation regimen. Immunosuppression is usually started during the deceased donor kidney transplant procedure. For elective living renal donor kidney transplantation, immunosuppression with a purine antagonist, such as azathioprine or mycophenolate mofetil, is commonly started a week before transplantation.

RECIPIENT OPERATION

The technique has become standardized over the past 50 years (Barry, 2007).

A prophylactic antibiotic, usually a cephalosporin, is administered just before surgery and is continued until the results of intraoperative cultures indicate a change or discontinuance. Fluoroquinolone antibiotics rapidly appear in renal cysts (Bennett et al, 1985), and one is commonly administered in place of the usual cephalosporin if polycystic kidneys are to be manipulated or removed at the time of transplantation.

A triple-lumen central venous pressure (CVP) line is commonly placed for blood draws, IV fluid administration, and CVP monitoring. A self-retaining balloon catheter is placed in the bladder and hooked to a 3-way system so that bladder irrigation with an antibiotic solution and bladder volume control for subsequent urinary tract reconstruction can be done. The CVP is maintained between 5 and 10 cm H_2O to provide adequate volume for renal perfusion.

The kidney graft is usually placed extraperitoneally in the contralateral iliac fossa through a modified Gibson incision so that the renal pelvis and ureter are the most medial and superficial of the hilar structures in case subsequent surgery on the collecting system of the kidney graft is necessary. In men, the spermatic cord is preserved. In women, the round ligament is ligated and divided. The peritoneum is retracted medially. The iliac arteries are palpated, and a suitable site for the arterial anastomosis is selected. Three soft spots are sought, one for the anastomosis and one for each of the vascular clamps. The latter to prevent plaque fracture and intimal dissection. The commonest arterial anastomosis is renal artery or, in the case of a deceased donor kidney transplant, an aortic patch, to the side of the external iliac artery. An aortic punch is usually employed to create a smooth, round hole in the recipient artery. The renal vein is usually anastomosed to the side of the external or common iliac vein.

In the rare instance of an orthotopic kidney transplant, left nephrectomy is performed, and the renal vein and splenic artery are used for renal revascularization.

Dual renal transplantation of marginal kidneys can be done by placing one in each iliac fossa, or stacking them, one on top of the other in the same iliac fossa (Ekser et al, 2010).

In small children, the aorta and IVC are commonly used for the vascular anastomoses.

Furosemide and mannitol are given intravenously during and immediately after renal revascularization to promote a diuresis.

Urinary tract reconstruction is usually by extravesical ureteroneocystostomy. See Table 36–7 for urinary tract reconstruction problems and how to deal with them. Double-pigtail ureteral stents are commonly used, as is a suction drain. If an anuric patient had a normal bladder before urine

Table 36–7. Urologic problems encountered at surgery and what to do about them.

Problems	Solutions
Continent chimney	Make incision lateral to stoma Place transplant in opposite iliac fossa
Scarred pelvis	3-way bladder catheter system to find bladder
Watertight reconstruction?	3-way catheter system to fill bladder and check for leak
Defunctionalized bladder	3-way catheter system to refill bladder late in case Shanfield or MacKinnon–Taguchi ureteroneocystostomy *or* Ureteroureterostomy (transplant ureter to native ureter) Pyeloureterostomy (transplant pelvis to native ureter)
Augmented bladder	Know the blood supply and avoid it
	Know the metabolic abnormality and treat it, if necessary
Gastrocystoplasty bleeding	Hydrogen ion pump blocker

production ceased, the bladder would regain its normal volume within 6 weeks, and pretransplant bladder cycling would be unnecessary.

POSTOPERATVE CARE

Intravenous fluid is given at a rate equal to the urinary output plus insensible loss. Boluses are given for hypotension. Recommendation for blood transfusion is if the hematocrit is under 25 and the patient is symptomatic, or when the hematocrit is less than 20. Delayed graft function is managed by raising the CVP to 10 cm H_2O and administering intravenous furosemide. Serum electrolytes and hematocrit are monitored every few hours until the values become stable. When the serum potassium is in the midnormal range, potassium is added to the IV solution. Hyperkalemia or fluid overload is usually managed by dialysis. High plasma potassium levels can be counteracted by intravenous calcium chloride, and the level of plasma potassium can be temporarily lowered by intravenous sodium bicarbonate and/or glucose and insulin. Bowel continuity usually returns within 3 days.

A urine culture is obtained 24 hours before catheter removal, and antibiotics are started or changed according to organism identity or sensitivity testing. When urinary tract reconstruction has been uncomplicated, the retention catheter is usually removed on the third postoperative day. A single oral dose of an α-blocker may prevent urinary retention at the time of bladder catheter removal. If external skin sutures or staples were used, they are removed 2–4 weeks postoperatively. If a ureteral stent was used and not secured to the bladder catheter, it is removed 4–12 weeks after the transplant procedure. A prophylactic urinary antibiotic such as trimethoprim-sulfamethoxazole (TMP/SMX) is commonly administered for 3 months. Minor sulfa allergy can be managed by desensitization during the transplant hospitalization. Major sulfa allergy is usually managed by substitution with a single, daily dose of nitrofurantoin.

COMPLICATIONS

A. Delayed Graft Function

When delayed graft function occurs, and the measures described above fail, ultrasonography with or without a radioisotope renogram is done to determine kidney graft blood flow and function and to screen for ureteral obstruction or fluid collections. Sometimes a biopsy is necessary to sort things out

B. Kidney Transplant Rejection

Rejection crises are suspected by increased plasma creatinine levels in the absence of hydronephrosis or urinary tract infection (UTI), usually confirmed by needle biopsy, and treated with increased doses of a glucocorticoid. Glucocorticoid-resistant cellular rejection is usually treated with lymphocyte-depleting antibody. Antibody-mediated rejection is managed with plasmapheresis, intravenous immunoglobulin, increased glucocorticoid, and sometimes rituximab, an anti-CD20 antibody.

C. Immunosuppression Side Effects

The most frequent complication from azathioprine or mycophenolate mofetil is leukopenia, and peripheral blood leukocyte counts are monitored with decreasing frequency. The most common complication of calcineurin inhibitors is nephrotoxicity, and blood levels of these drugs are also monitored with decreasing frequency. Nephrotoxic drugs, such as aminoglycosides and amphotericin B, and potassium-sparing diuretics should be used with caution in patients receiving tacrolimus or cyclosporine. Hypogonadism is a side effect of mTOR inhibitors (Lee et al, 2005).

D. Hematuria

Acute postoperative hematuria that cannot be controlled by catheter irrigation is managed by endoscopic fulguration or, rarely, open surgery.

E. Hemorrhage

Unless the kidney tamponades without ureteral obstruction or vascular obstruction, graft exploration is necessary.

F. Graft Rupture

This is rare, due to severe, acute rejection or renal vein thrombosis, and allograft nephrectomy is usually necessary.

G. Renal Artery Stenosis

This is suspected with the development of severe, poorly controlled hypertension and decreased renal function. Screening is done with Doppler flow studies, and diagnosis is by renal arteriogram. Treatment is usually by transluminal angioplasty and an intra-arterial stent.

H. Fluid Collection with or without Hydronephrosis

The composition of the fluid can be determined by aspirate examination. Pus is drained, and antibiotics are initiated. If the aspirate is clear, and the creatinine level is the same as that of serum, the fluid is from a lymphocele. It can be aspirated a time or two, and, if persistent, it can be treated with percutaneous sclerosis or by unroofing it into the peritoneal cavity. If the creatinine level of the fluid is high, it is a urinoma. The source of a urine leak can be determined by cystogram and/or percutaneous nephrostogram. Bladder leaks can be managed by catheter drainage for a week and repeating a cystogram to ensure healing before catheter removal. If a ureteral leak is diagnosed, initial treatment is usually a percutaneous nephrostomy tube and a drain. Sometimes the leak can be managed by a ureteral stent to bridge the defect while it heals, and open surgical repair is saved until minimally invasive therapy has failed. If ureteral necrosis is the cause of the urinoma, open repair will be necessary.

I. Wound Infection

This is prevented largely by the prophylactic measures mentioned previously. When it occurs, treatment is with drainage and antibiotics. For severe infections, the purine antagonist is withheld, the glucocorticoid dose is reduced, and the calcineurin inhibitor is continued.

J. Urinary Tract Infection

Urinary tract infection following renal transplantation is common. The risk factors of indwelling urinary catheter, age, and immunosuppression are always present, and urinary retention and diabetes mellitus are additional factors. Episodes of graft dysfunction accompanied by fever can be due to acute rejection or allograft pyelonephritis, and the two must be differentiated from one another because increased immunosuppression during a bout of untreated pyelonephritis can result in fatal sepsis. Urinary tract infections that occur months after transplantation are usually benign and respond to standard antimicrobial therapy. Asymptomatic bacteriuria does not need to be treated (Origuen et al, 2016).

K. Other Infections

Although pneumonia can be due to common bacterial organisms, *Legionella, Nocardia,* mycobacteria, viruses, parasites, and fungi can all be etiologic agents.

L. Renal Calculi

These can be managed by extracorporeal shockwave lithotripsy, percutaneous nephrostolithotomy, or ureterorenoscopy. Ureteroscopic management can be simple if a refluxing ureteroneocystostomy, native ureteroureterotomy, or native ureteropyelostomy was the technique for renal transplant urinary tract reconstruction, or problematic in the case of an antireflux ureteroneocystostomy with a tortuous distal ureter. Stone etiology can be renal tubular acidosis, preexisting stone disease in the transplanted kidney, urinary tract infection, or persistent hyperparathyroidism. The last may necessitate subtotal parathyroidectomy and forearm implantation of parathyroid tissue.

M. Deep-Vein Thrombosis and Pulmonary Embolism

Standard anticoagulation protocols are used to prevent and treat these disorders.

N. Posttransplant Hypertension

Causes for this are intrinsic renal disease, rejection, transplant renal artery stenosis, and calcineurin inhibitor toxicity.

O. Vascular Disease

Myocardial infarction and stroke continue to be leading causes of death in this patient population despite aggressive preoperative assessment and treatment. Glucocorticoid immunosuppression increases cardiovascular risk because of hyperlipidemia, and posttransplant hyperlipidemia is treated with dietary changes and antilipid medications.

P. New-Onset Diabetes Mellitus

This occurs in a significant proportion of renal transplant recipients because of the diabetogenic effects of glucocorticoids and calcineurin inhibitors and the restoration of renal function. Patients with diabetes responsive to oral hypoglycemics before transplantation usually require insulin therapy after transplantation, and patients who required insulin prior to transplantation may require twice the insulin dosage afterward.

Q. Urologic Malignancy

When compared with the general population, transplant recipients have increased standardized incidence ratios (SIR) of infection-related cancers, such as lymphoproliferative disorders, Kaposi's sarcoma, and carcinomas of the oropharynx, stomach, anus, cervix, penis, vulva, and vagina (Engels et al, 2011).

The overall cancer-specific SIRs for kidney and bladder cancers have been reported to be 8.61 and 3.18, respectively, and the overall SIR of prostate cancer to be 1.11 (Yan et al, 2014).

When pelvic malignancy surgery is done, it's best not to do a lymph node dissection on the side of the transplant because of the risk to the kidney graft's blood supply and urinary tract reconstruction.

Consult with transplant medicine before prescribing immunotherapy for a urologic malignancy in an immunosuppressed transplant recipient. Agents that stimulate the immune system (eg, checkpoint inhibitors) or are infection-causing immune stimulants (bacillus Calmette–Guerin [BCG]) are usually contraindicated.

CONCLUSIONS

Renal transplantation can be successfully performed in ESRD patients who are carefully selected and who have major risk factors treated prior to transplantation. The use of low-score KDPI kidneys for low-score EPTS recipients may balance equity and justice in the distribution of deceased donor organs. Kidney donation from living donors requires the application of criteria for donor safety and renal quality. The major surgical problems are due to arteriosclerosis, urinary tract abnormalities, and technical misadventures. Posttransplant infectious complications have been reduced by immunizations, donor assessment, prophylactic anti-infective agents, and the careful selection of immunosuppression regimens.

BIBLIOGRAPHY

Barry JM, et al: Renal transplantation. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (eds): Campbell-Walsh Urology. 10th ed. Elsevier, Philadelphia, 2012, pp. 1238–1239.

Barry JM: Renal transplant recipient surgery. BJU Int 2007;99(3): 701–717.

Bennett WM, et al: Cystic fluid antibiotic concentrations in autosomal-dominant polycystic kidney disease. Am J Kidney Dis 1985;6(6):400–404.

Centers for Disease Control and Prevention: Recommended immunization schedules for children, teens, and adults. CDC, 2018. (Available online at: http://www.cdc.gov/vaccines.)

Charlson Comorbidity Index (CCI)—MDCalc. (Available online at: www.mdcalc/charlson-comorbidity-index-cci; accessed 7/13/18.)

Ekser B, et al: Technical aspects of unilateral dual kidney transplantation from expanded criteria donors: Experience of 100 patients. Am J Transplant 2010;10(9):2000–2007.

Engels EA, et al: Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306(17):1891–1901.

Grams ME, et al: Listing for expanded criteria donor kidneys in older adults and those with predicted benefit. Am J Transplant 2010;10(4):802–809.

Hautmann RE, et al: The ileal neobladder: Complications and functional results in 363 patients after 11 years of follow-up. J Urol 1999;161(2):422–427.

Kuroda N, et al: Review of acquired cystic disease-associated renal cell carcinoma with focus on pathobiological aspects. Histol Histopathol 2011;26(9):1215–1218.

Lee S, et al: The effect of sirolimus on sex hormone levels of male renal transplant recipients. Clin Transplant 2005;19(2):162–167.

Lentine KL, et al: Summary of Kidney Disease Global Outcomes (KDIGO) clinical practice guideline on the evaluation and care of living kidney donors. Transplantation 2017;101(6):1783–1792.

Monga M: Maternal cardiovascular and renal adaptation in pregnancy. In: Creasy RK, Resnik R (eds): Maternal-Fetal Medicine. 4th ed. Saunders, Philadelphia, 1998, pp. 787–788.

Muzaale AD, et al: Risk of end-stage renal disease following live kidney donation. JAMA 2014:311(6):579–586.

Newell KA, et al: Integrating APOL1 gene variants into renal transplantation: Considerations arising from the American Society of Transplantation Expert Conference. Am J Transplant 2017;17(4):901–911.

Origuen J, et al: Should asymptomatic bacteriuria be systematically treated in kidney transplant recipients? Results of a randomized controlled trial. Am J Transplant 2016;16(10):2943–2953.

Segev DL, et al: Perioperative mortality and long-term survival following live kidney donation. JAMA 2010;303(10):959–966.

Seigel RL, et al: Cancer statistics, 2018. CA Cancer J Clin 2018;68(1): 7–30.

Smith RA, et al: Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening, 2018. (Available online at: http://doi.org/10.3322/caac.21446.)

United States Renal Data System: 2017 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2017.

Wolfe RA, et al: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of first cadaver kidney transplants. New Engl J Med 1999;341(23):1725–1730.

Yan L, et al: Risk of bladder cancer in renal transplant recipients: A meta-analysis. Br J Cancer 2014;110(7):1871–1877.

Yoon SC, Hurst FP, Jindal RM, et al: Trends in renal transplantation in patients with human immunodeficiency virus infection: An analysis of the United States renal data system. Transplantation 2011;91(8): 864–868.

Disorders of the Ureter and Ureteropelvic Junction

37

Barry A. Kogan, MD

The ureter is a complex functional conduit carrying urine from the kidneys to the bladder. Any pathologic process that interferes with this activity can cause renal abnormalities; the most common sequels are hydronephrosis (see Chapter 14) and infection. Disorders of the ureter can be classified as congenital or acquired.

CONGENITAL ANOMALIES OF THE URETER

Congenital ureteral malformations are common and range from complete absence to duplication of the ureter. They may cause severe obstruction requiring urgent attention, or they may be asymptomatic and of no clinical significance. The nomenclature can be confusing and has been standardized to prevent ambiguity (Glassberg et al, 1984).

URETERAL ATRESIA

The ureter may be absent entirely, or it may end blindly after extending only part of the way to the flank. These anomalies are caused during embryologic development, by failure of the ureteral bud to form from the mesonephric duct or by an arrest in its development before it contacts the metanephric blastema. The molecular and genetic determinants of bud development and the causes of bud abnormalities are complex but are being elucidated (Nagalakshmi and Yu). In any event, the result of an atretic ureteral bud is an absent or multicystic dysplastic kidney. The multicystic kidney is usually unilateral and asymptomatic and of no clinical significance. In rare cases, it can be associated with hypertension, infection, or tumor. Contralateral vesicoureteral reflux is common, but usually of limited clinical significance. There has been a concern about the risk of malignancy in these cases; however, the preponderance of evidence now suggests that no treatment is necessary and indeed no follow-up is needed from a urological standpoint (Onal and Kogan, 2006).

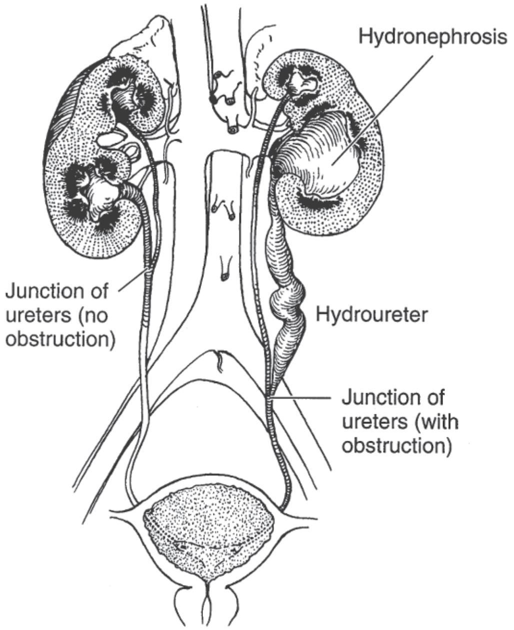
DUPLICATION OF THE URETER

Complete or incomplete duplication of the ureter is one of the most common congenital malformations of the urinary tract. Nation (1944) found some form of duplication of the ureter in 0.9% of a series of autopsies. The condition occurs more frequently in females than in males and is often bilateral.

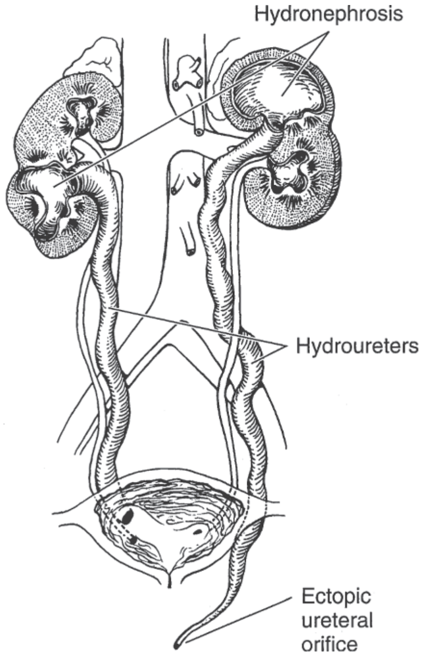
The incomplete (Y) type of duplication is caused by branching of the ureteral bud before it reaches the metanephric blastema. In most cases, this anomaly is associated with no clinical abnormality. However, disorders of peristalsis may occur near the point of union (Figure 37–1).

In complete duplication of the ureter, the presence of two ureteral buds leads to the formation of two totally separate ureters and two renal pelves. Because the ureter to the upper segment arises from a cephalad position on the mesonephric duct, it remains attached to the mesonephric duct longer and consequently migrates farther, ending medial and inferior to the ureter draining the lower segment (Weigert–Meyer law). Thus, the ureter draining the upper segment may migrate too far caudally and become ectopic and obstructed, whereas the ureter draining the lower segment may end laterally and have a short intravesical tunnel that leads to vesicoureteral reflux (Figure 37–2) (Tanagho, 1976). More recent studies have suggested that apoptosis of the common nephric duct cells is essential for separation of the ureter from the Wolffian duct; failure of this likely is the root cause of an ectopic ureter (Mendelsohn et al, 2009). Moreover, it is the urogenital sinus that induces this apoptosis and separation, and it appears that the upper ureteral bud may, in some cases, be too far from the urogenital sinus to receive the signal, thereby failing to separate from the Wolffian duct.

Although many patients with duplication of the ureter are asymptomatic, a common presentation is persistent or recurrent infections. In females, the ureter to the upper pole may be ectopic, with an opening distal to the external sphincter or even outside the urinary tract. Such patients have classic


Hydronephrosis
Junction of ureters (no obstruction)
Hydroureter
Junction of ureters (with obstruction)

▲ **Figure 37–1.** Duplication of the ureter. Incomplete (Y) type with hydronephrosis of lower pole of left kidney. Ureteroureteral (yo-yo) reflux can also occur and account for the radiographic appearance.



▲ **Figure 37–2.** Duplication of the ureter. Complete duplication with reflux to lower pole of right kidney and chronic pyelonephritic scarring. Upper pole ureter of left kidney is ectopic, and its associated renal parenchyma is often dysplastic.

symptoms: incontinence characterized by constant dribbling and at the same time, a normal pattern of voiding. In males, because the mesonephric duct becomes the vas and seminal vesicles, the ectopic ureter is always proximal to the external sphincter, and associated incontinence does not occur. In recent years, prenatal ultrasonography has led to the diagnosis in many asymptomatic neonates.

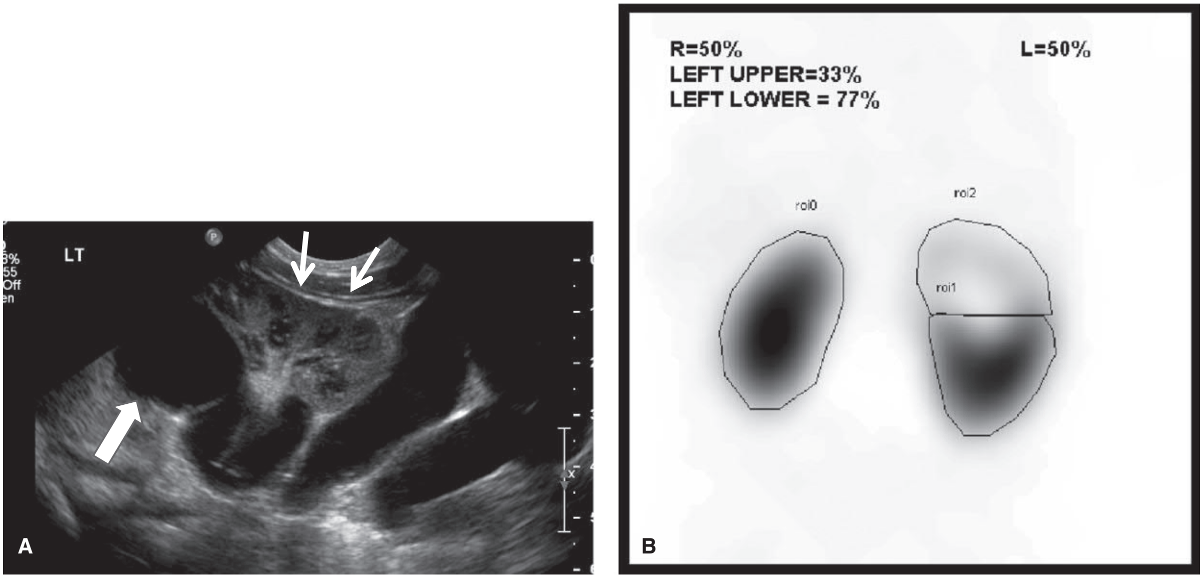
At the present time, ultrasound is the study of choice in these children. Generally, a hydronephrotic upper pole and a dilated distal ureter are seen, and in addition, one can readily evaluate parenchymal thickness and the presence of a ureterocele or other bladder anomalies. A voiding cystourethrogram is important to determine the presence of vesicoureteral reflux and confirm a ureterocele, if present. Renal scanning (especially with ^{99m}Tc-di(mercaptosuccinic acid) can be helpful for estimating the degree of renal function in each renal segment (Figure 37–3).

The treatment of reflux is controversial (Chapter 13), but the treatment should not be influenced by the presence of ureteral duplication. Lower grades of reflux are generally treated nonoperatively, and higher grades of reflux are more likely to be treated surgically. Because of anatomic variations, many surgical options are available. If upper pole obstruction or ectopy is present, surgery is almost always required. Numerous operative approaches have been recommended (Belman et al, 1974). If renal function in one segment is very poor, heminephrectomy is the most appropriate procedure. In an effort to preserve renal parenchyma, treatment by pyeloureterostomy, ureteroureterostomy, and ureteral reimplantation are all appropriate (Amar, 1970). This can be done laparoscopically or open (Howe et al, 2017).

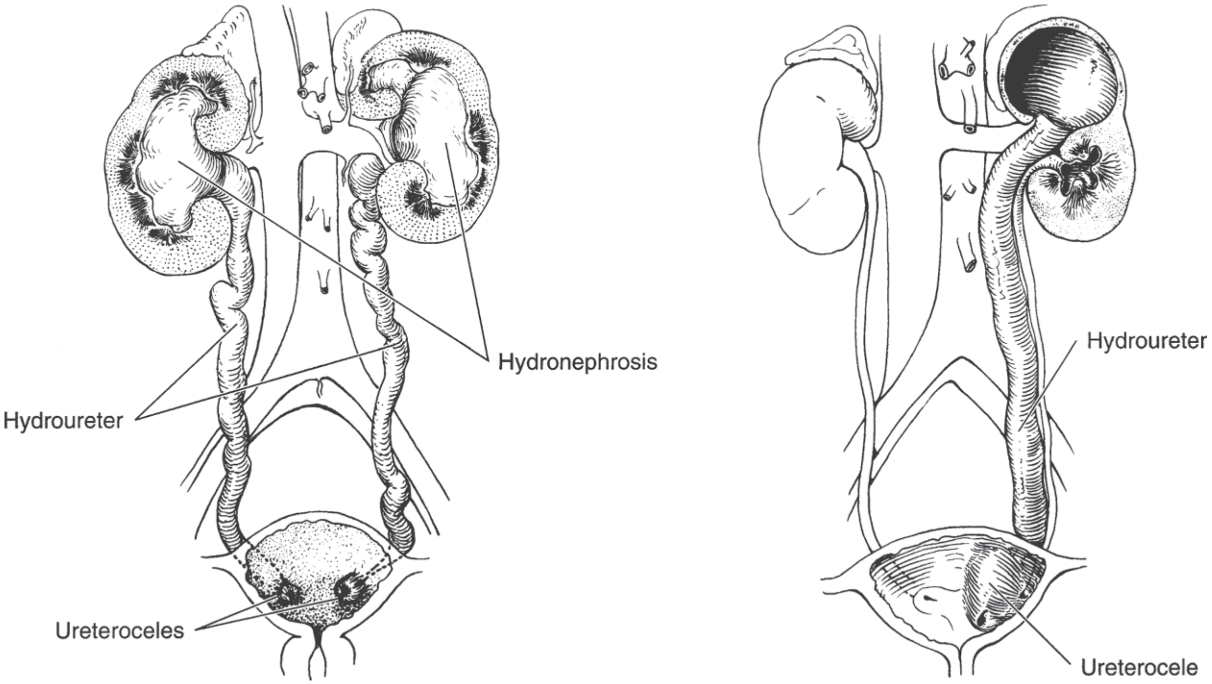
URETEROCELE

A ureterocele is a sacculation of the terminal portion of the ureter (Figure 37–4). It may be either intravesical or ectopic; in the latter case, some portion is located at the bladder neck or in the urethra. Intravesical ureteroceles are associated most often with single ureters (and if so, more often in boys), whereas ectopic ureteroceles nearly always involve the upper pole of duplicated ureters. Ectopic ureteroceles are 4 times more common than those that are intravesical (Snyder and Johnston, 1978). Ureterocele occurs 7 times more often in girls than in boys, and about 10% of cases are bilateral. Mild forms of ureterocele are found occasionally in adults examined for unrelated reasons.

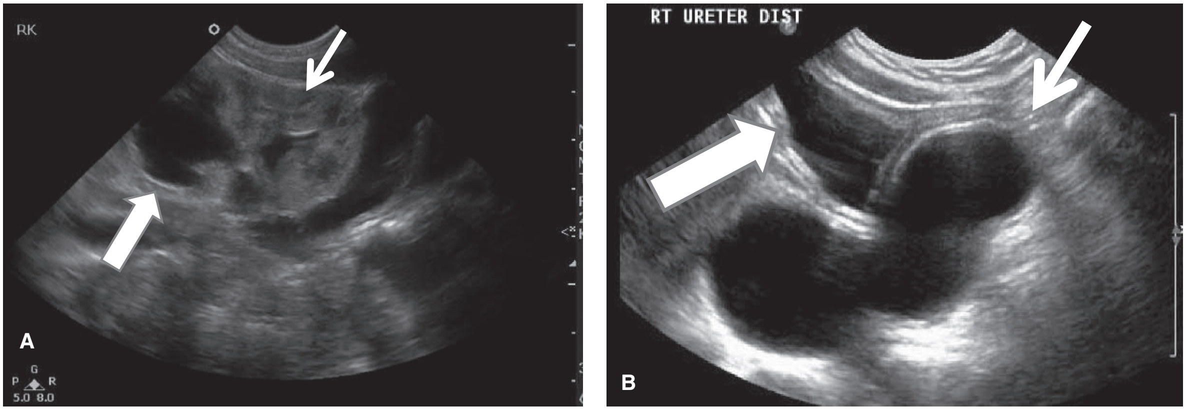
Ureterocele has been attributed to delayed or incomplete canalization of the ureteral bud leading to an early prenatal obstruction and expansion of the ureteral bud prior to its absorption into the urogenital sinus (Tanagho, 1976).



▲ **Figure 37–3.** Duplicated left kidney. ***A:*** Ultrasound showing marked hydronephrosis of the left upper pole (*large arrow*) in continuity with a large tortuous ureter. The lower pole of the kidney is well preserved (*small arrows*). ***B:*** ^{99m}Tc-DMSA scan showing the relative function of the different renal segments.



▲ **Figure 37–4.** Ureterocele. ***Left:*** Orthotopic ureterocele associated with a single ureter. ***Right:*** Ureterocele associated with ureteral duplication and poor function of upper pole of kidney.

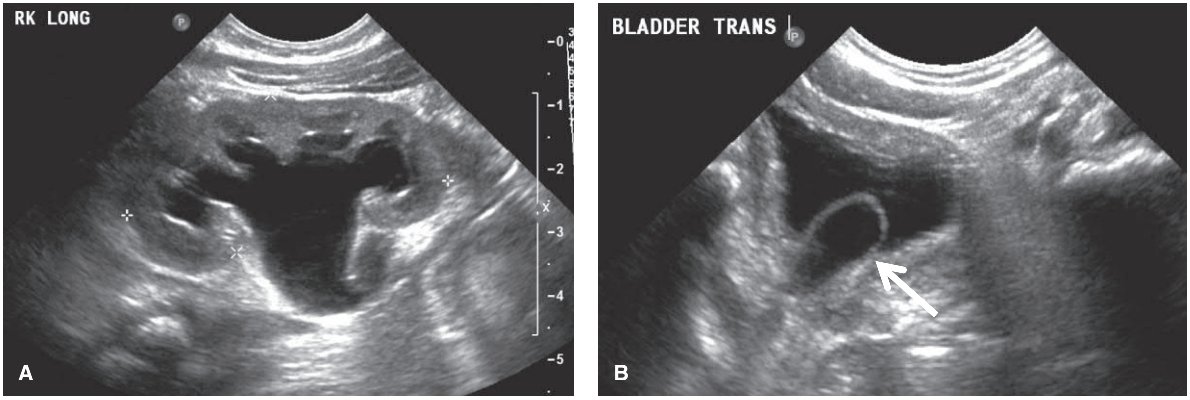


▲ **Figure 37–5.** Ureterocele in a girl with a duplication. ***A:*** Ultrasound showing marked hydronephrosis of the right upper pole (*large arrow*). The lower pole of the kidney is well preserved (*small arrow*). ***B:*** In contrast to an ectopic ureter, the dilated distal right ureter ends in a large ureterocele (*small arrow*) within the bladder (*large arrow*).

The cystic dilation forms between the superficial and deep muscle layers of the trigone. Large ureteroceles may displace the other orifices, interfere with the muscular backing of the bladder, or even obstruct the bladder outlet. There is nearly always significant hydroureteronephrosis, and dysplasia of the upper pole of the kidney may be found in association with an ectopic ureterocele.

Clinical findings vary considerably. In the past, patients presented with infection, bladder outlet obstruction, or incontinence (and, rarely, a ureterocele may prolapse through the female urethra). However, most of the current cases are diagnosed by antenatal maternal ultrasound. After birth, sonography and voiding cystourethrography should be performed. The former confirms the diagnosis and defines the renal anatomy; the latter demonstrates whether there is reflux into the lower pole or contralateral ureter or rarely into a spontaneously ruptured ureterocele (Figures 37–5 and 37–6). Renal scanning is helpful for estimating renal function, and the combination of findings is critical in planning therapy.

Treatment must be individualized. Transurethral incision has been recognized as the definitive procedure in many instances, particularly in patients with intravesical ureteroceles and may be the initial therapy in neonates. When an open operation is needed, selection of the procedure must be based on the anatomic location of the ureteral meatus, the position of the ureterocele, and the degree of hydroureteronephrosis and impairment of renal function. In general, choices range from heminephrectomy and ureterectomy to excision of the ureterocele, vesical reconstruction, and ureteral reimplantation. Some have even recommended upper pole ureteral ligation, a procedure that can be done laparoscopically with minimal morbidity (Lopes et al, 2018). Often, more than one procedure is necessary.



▲ **Figure 37–6.** Ureterocele in a boy with a single system. ***A:*** Ultrasound showing moderate right hydronephrosis with a dilated proximal ureter. ***B:*** The right distal ureter ends in a small orthotopic ureterocele within the bladder (*arrow*).

ECTOPIC URETERAL ORIFICE

Although an ectopic ureteral orifice most commonly occurs in association with duplication of the ureter (see preceding sections), single ectopic ureters do occur. They are caused by a delay or failure of separation of the ureteral bud from the mesonephric duct during embryologic development. An excellent review of current studies of ureteral bud development has been published (Nagalakshmi and Yu, 2015). In anatomic terms, the primary anomaly may be an abnormally located ureteral bud; that also explains the high incidence of dysplastic kidneys associated with single ectopic ureters.

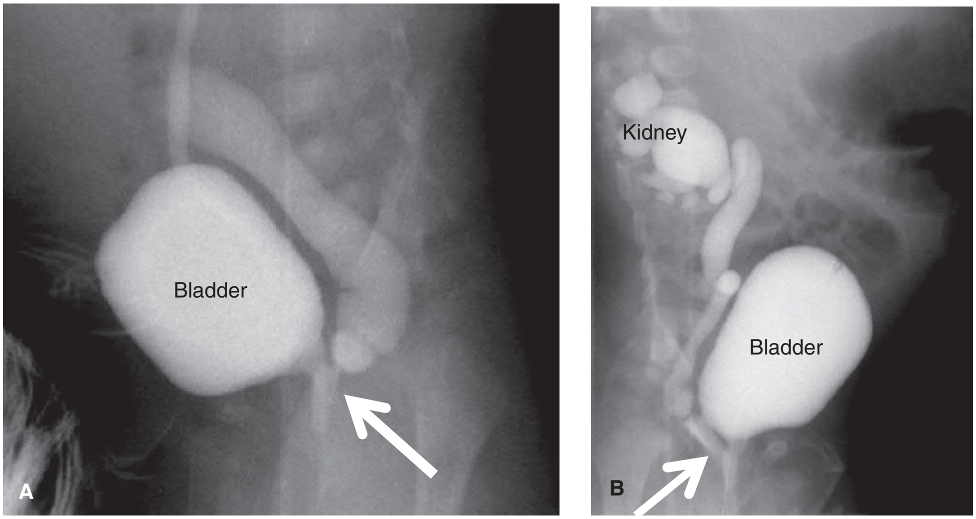
The clinical picture varies according to the gender of the patient and the position of the ureteral opening. Boys are seen because of urinary tract infection or epididymitis. In these cases, the ureter may drain directly into the vas deferens or seminal vesicle. In girls, the ureteral orifice may be in the urethra, vagina, or perineum. Although infection may be present, incontinence is the rule. Continual dribbling despite normal voiding is pathognomonic, but urgency and urge incontinence may confound the diagnosis.

Sonography and voiding cystourethrography help delineate the problem. If the ureter is ectopic to the urethra, the ectopic ureter may be seen on the voiding film from the voiding cystourethrography (Figure 37–7). However, because an ectopic kidney may be both tiny and in an abnormal location, it may be difficult to find by ultrasound; magnetic resonance imaging, cystoscopy, or laparoscopy may be necessary to confirm the diagnosis (Lipson et al, 2008). During cystoscopy, a hemitrigone may be seen, and the ectopic orifice may be visualized directly or demonstrated by retrograde catheterization. Renal scanning is also helpful in estimating relative renal function. As in ureteroceles and duplication of the ureter, the clinical picture and the degree of renal function dictate the therapeutic approach.

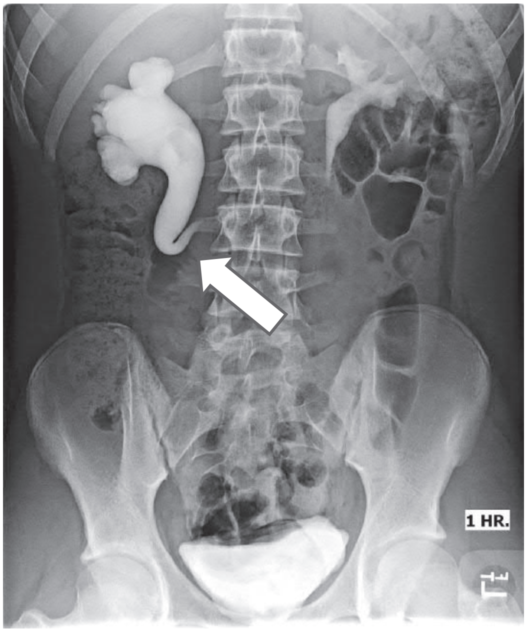
ABNORMALITIES OF URETERAL POSITION

Retrocaval ureter (also called **circumcaval ureter** and **postcaval ureter**) is a rare condition in which an embryologically normal ureter becomes entrapped behind the vena cava because of abnormal persistence of the right subcardinal (as opposed to the supracardinal) vein. This forces the right ureter to encircle the vena cava from behind. The ureter descends normally to approximately the level of L3, where it curves back upward in the shape of a reverse J to pass behind and around the vena cava (Figure 37–8). Obstruction generally results.

The diagnosis of retrocaval ureter was, in the past, usually made by excretory urography. However, since sonography is now usually the first test performed, the radiologist must be suspicious of the anomaly based on a dilated proximal (but not distal) ureter. Currently, magnetic resonance imaging may be the best single study to delineate the anatomy clearly and noninvasively. Surgical repair for retrocaval ureter, when indicated, consists in dividing the ureter (preferably across the dilated portion), bringing the distal ureter from behind the vena cava, and reanastomosing it to the proximal end. The procedure has been performed laparoscopically to reduce morbidity (Bagheri et al, 2009.



▲ **Figure 37–7.** Ectopic ureter. ***A:*** Voiding cystourethrogram in a boy showing voiding into the posterior urethra with reflux into a very dilated ureter, seen entering the prostatic urethra (*arrow*). ***B:*** A voiding cystourethrogram in a girl showing voiding with reflux into a very dilated ureter and continuing all the way up to a dilated lower pole of the right kidney. Note that the ureter is ectopic, entering the proximal urethra (*arrow*).

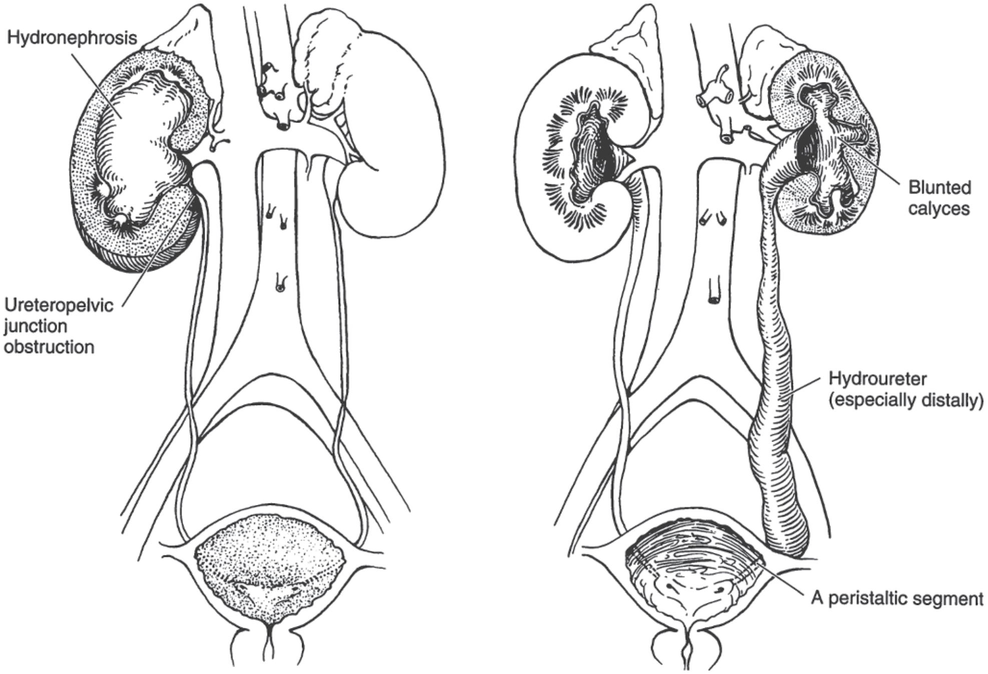


▲ **Figure 37–8.** Retrocaval ureter. An intravenous urogram showing the classic appearance of a J-hooking of the ureter behind the inferior vena cava (*arrow*).

OBSTRUCTION OF THE URETEROPELVIC JUNCTION

In children, primary obstruction of the ureter usually occurs at the ureteropelvic junction or the ureterovesical junction (Figure 37–9). Obstruction of the ureteropelvic junction is probably the most common congenital abnormality of the ureter. In children, it is seen more often in boys than in girls (5:2 ratio). In contrast, it has become clear that in adults, it is more common in women than in men (Capello et al, 2005). In unilateral cases, it is more often on the left than on the right side (5:2 ratio). Bilateral obstruction occurs in 10–15% of cases and is especially common in infants (Johnston et al, 1977). The abnormality may occur in several members of the same family, but it shows no clear genetic pattern.

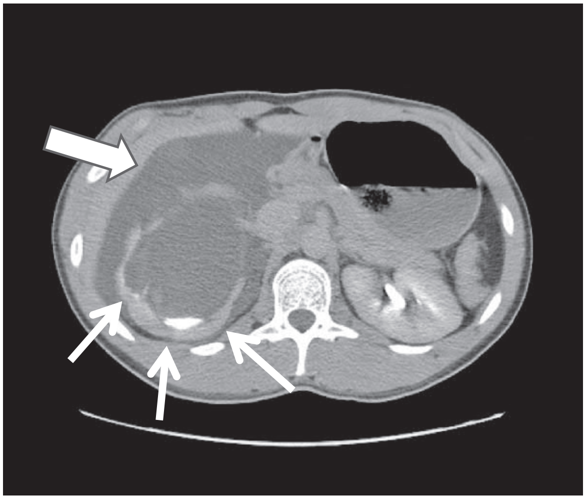
The exact cause of obstruction of the ureteropelvic junction seldom is clear. Ureteral polyps and valves are seen but are rare. There is almost always an angulation and kink at the junction of the dilated renal pelvis and ureter. This by itself can cause obstruction, but it is unclear whether this is primary or merely secondary to another obstructive lesion. True stenosis is found rarely; however, a thin-walled, hypoplastic proximal ureter is observed frequently. Characteristic histologic and ultrastructural changes are observed in this area and could account for abnormal peristalsis through the ureteropelvic junction and consequent interference with pelvic


Hydronephrosis
Ureteropelvic junction obstruction
Blunted calyces
Hydroureter (especially distally)
A peristaltic segment

▲ **Figure 37–9.** Congenital ureteral obstruction. ***Left:*** Right ureteropelvic junction obstruction with hydronephrosis. ***Right:*** Left ureterovesical junction obstruction (obstructed megaureter) with hydroureteronephrosis.

emptying (Hanna et al, 1976). Current basic research suggests that decreased BMP4 signaling leads to disruption of smooth muscle investment of the ureter and may be involved (Wang et al, 2008). In addition, there seems to be an overexpression of extracellular matrix and depleted numbers of nerves, although in most series the findings are highly variable How et al, 2007; Kaya et al, 2010). Two other findings sometimes seen at operation are a high origin of the ureter from the renal pelvis and an abnormal relationship of the proximal ureter to a lower pole renal artery. It is debatable whether these findings are the cause or the result of pelvic dilatation, but Stephens (1982) has suggested that abnormal rotation of the renal pelvis allows the ureter to become entrapped in the blood vessels of the lower pole of the kidney, ultimately leading to obstruction. Using careful studies at the time of operation, it is usually possible to define whether the principal lesion is intrinsic or extrinsic (Johnston, 1969; Koff et al, 1986).

Clinical findings vary depending on the patient's age at diagnosis. Many cases are now diagnosed in utero. These tend to be primarily intrinsic lesions, and many resolve spontaneously. Later, pain and vomiting are the most common symptoms; however, hematuria and urinary infection also may be seen. A few patients have complications such as calculi, trauma to the enlarged kidney (Figure 37–10), or (rarely) hypertension. Most of the cases diagnosed in adults are extrinsic lesions and often in females, but it is unclear whether they originated from intrinsic problems earlier in development (Capello et al, 2005).



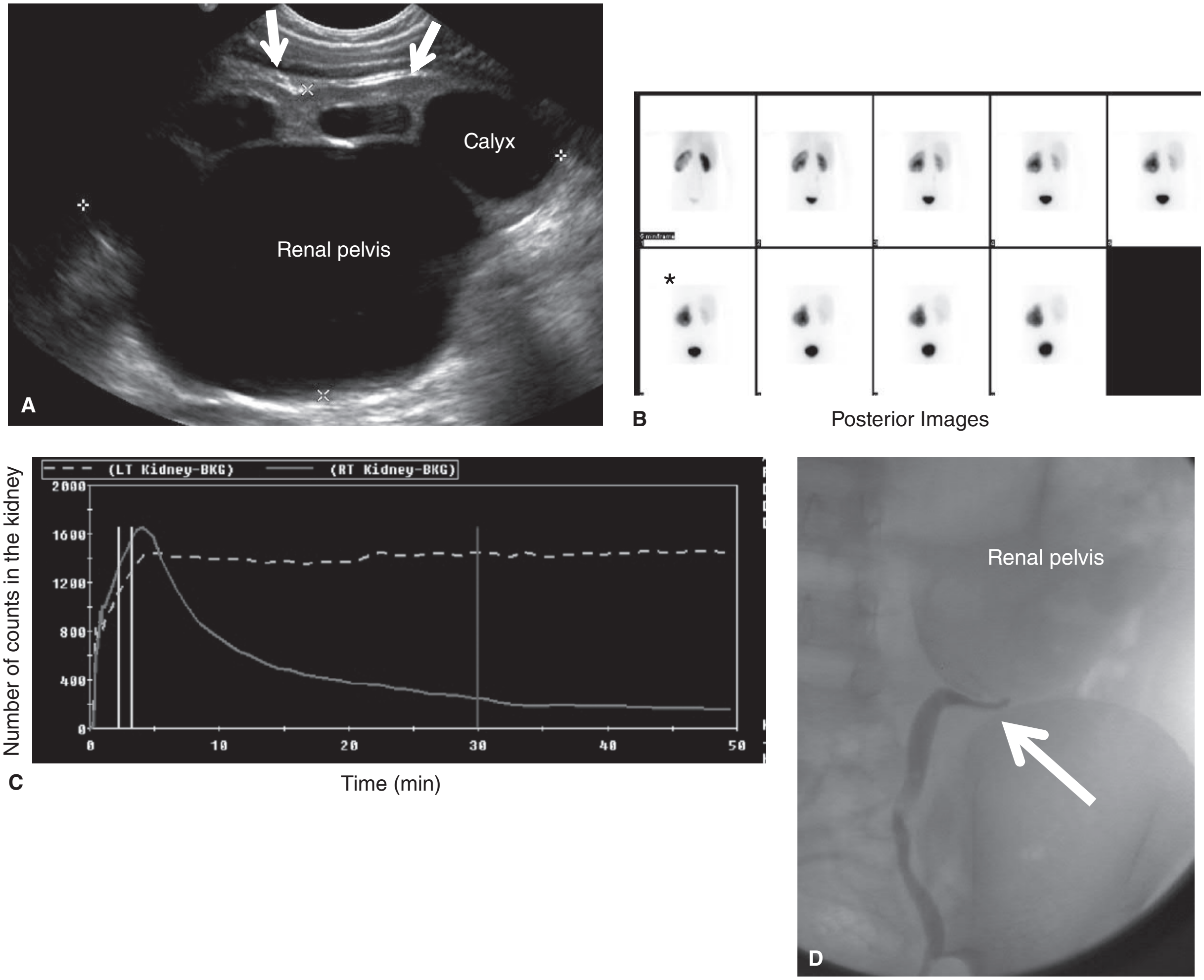
▲ Figure 37–10. Ureteropelvic junction obstruction discovered after trauma. CT scan in an 18-year-old boy performed after abdominal trauma shows a markedly hydronephrotic right kidney (*small arrows*) and a urinoma due to urinary extravasation from a rupture of the renal pelvis (*large arrow*).

The diagnosis is made most often by sonography. In equivocal cases, diuretic renography or (rarely) antegrade urography with pressure–flow studies is helpful (Thrall et al, 1981; Whitaker, 1973) (Figure 37–11). Some surgeons consider a voiding cystourethrogram to be a routine part of the preoperative workup, but it may not be needed unless the ureter is dilated (or both) below the ureteropelvic junction.

Symptomatic obstruction of the ureteropelvic junction should be treated surgically. Because most cases are now detected by hydronephrosis on prenatal ultrasonography and the infants are asymptomatic, it becomes important to assess the significance of the hydronephrosis. On one hand, early surgery may prevent future urinary tract infections, stones, or other complications; on the other hand, many of the patients could live their whole lives without experiencing a consequence of the hydronephrosis. This remains an area of considerable controversy. Early surgery is recommended for patients who have kidneys with diminished function, massive hydronephrosis, infection, or stones. Nonoperative surveillance is thought to be safe, although up to 25% of patients may ultimately require an operative repair for pain, urinary infection, or reduced renal function on repeat nuclear scan. Clinicians and scientists are searching for biomarkers of obstruction, and urinary proteome analysis seems promising (Drube et al, 2010). This subject remains particularly controversial, but there are some data suggesting that early childhood treatment reduces the risk of ureteropelvic junction obstruction in adults (Capello et al, 2005).

Because of anatomic variations, no single procedure is sufficient for all situations (Smart, 1979). Regardless of the technique used, all successful repairs have in common the creation of a dependent and funnel-shaped ureteropelvic junction of adequate caliber. Although preservation of the intact ureteropelvic junction is feasible in some circumstances, when the obstruction appears to be caused by a dyskinetic segment of proximal ureter, the most popular operation is a dismembered pyeloureteroplasty (Anderson, 1963). Dismembered pyeloureteroplasty is also favored when the proximal ureter is hooked over a lower pole blood vessel. When there is a dilated extrarenal renal pelvis, dismembered pyeloureteroplasty can be combined with a Foley Y-V plasty to create a more funnel-shaped ureteropelvic junction (Foley, 1937). Pelvic flap procedures (Culp and De, 1951) are suited ideally to cases in which the ureteropelvic junction has remained in a dependent position despite significant pelvic dilatation. They also have the advantage of interfering less with the ureteral blood supply; this is particularly relevant when distal ureteral surgery (eg, ureteral reimplantation) is contemplated in the future. In most centers, the dismembered pyeloureteroplasty is the mainstay of repairs.

Both the Y-V plasty and the flap techniques are useful in managing ureteropelvic junction obstructions in horseshoe or pelvic kidneys, in which the anatomy may prevent creation of a dependent ureteropelvic junction if a dismembered technique is attempted. The use of stenting catheters and



▲ **Figure 37–11.** Ureteropelvic junction obstruction after prenatal hydronephrosis. ***A:*** An ultrasound shows marked hydronephrosis with a large renal pelvis and dilated calyces. There is some preservation of renal parenchyma (*arrows*). ***B:*** Images taken every 5 minutes from the ^{99m}Tc-MAG3 diuretic renogram showing good function on the left kidney, but hydronephrosis and slow drainage from the kidney. The *asterisk* indicates when furosemide is given. Of note, there is no increase in drainage from the left kidney after furosemide. ***C:*** The computer-calculated time/activity curves from the renogram pictures. Both kidneys have good function (high counts in the first couple of minutes). The right kidney (*solid line*) excretes the radioisotope rapidly. There is poor drainage of the left kidney (*dotted line*). ***D:*** A retrograde pyelogram demonstrates a normal ureter with obstruction at the ureteropelvic junction (*arrow*) and a large renal pelvis above the obstruction.

proximal diversion at the time of pyeloplasty has been the subject of debate, and the issue has not been resolved. Excellent results have been reported both with and without stents and diversions (Smith et al, 2002).

The prognosis is generally good. In many cases, postoperative ultrasound confirms the success (Kern et al, 2017). In several large series, the reported reoperation rate has been only 2–4%, but the postoperative radiographic appearance of the area may be disappointing. There can be marked improvement when a large extrarenal pelvis has prevented massive calyceal distortion; however, in some cases, considerable deformity persists despite adequate drainage of the kidney. In these cases, postoperative diuretic renography is helpful in confirming operative success. In some cases, it takes many years before the radiographic appearance improves.

The progressive move to minimally invasive surgery has resulted in a major change in management. Endopyelotomy can be performed percutaneously or via ureteroscopy and treats the problem by incising directly through the obstruction, stenting the area, and allowing healing via secondary intention. The technique is similar to that reported by Davis (1943) but is done entirely endoscopically. Unfortunately, the success rate is only 80% at best, and although popular, it should be used primarily for cases that have failed an initial repair (Jacobs et al, 2018). Another selected indication is when there are stones in the kidney with a ureteropelvic junction obstruction. Both conditions can be corrected within one endoscopic procedure. However, these procedures have been largely supplanted by laparoscopic repair. In particular, the remarkable growth of robotic urological surgery has allowed for many more surgeons to become proficient with robot-assisted pyeloplasty, and this has become a preferred option. Although morbidity is similar compared to open surgery and is more expensive, there is an obvious cosmetic advantage, especially in older children and adults (Howe et al, 2017; Chan et al, 2017).

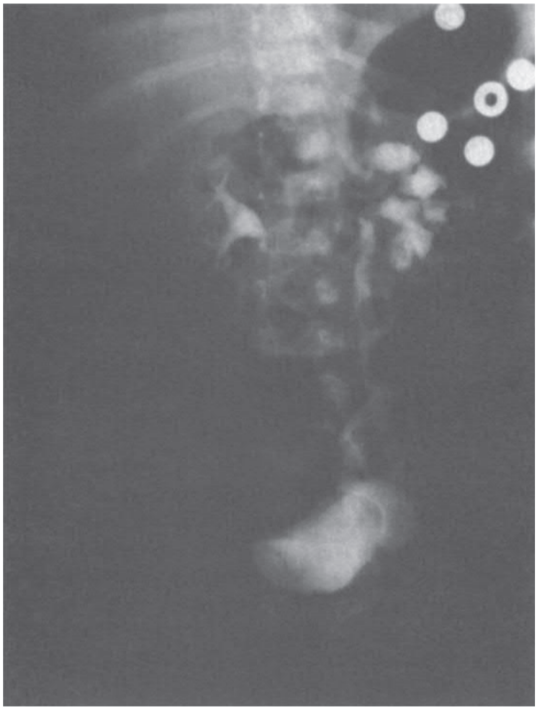
OBSTRUCTED MEGAURETER

Obstruction at the ureterovesical junction is 4 times more common in boys than in girls. It may be bilateral and is usually asymmetric. The left ureter is slightly more often involved than the right.

The embryogenesis of the lesion is uncertain. In most cases, there is no stricture at the ureterovesical junction. At operation, a retrograde catheter or probe can usually be passed through the area of obstruction. Close observation either at operation or by fluoroscopy reveals a failure of the distal ureter to transmit the normal peristaltic wave, resulting in a functional obstruction. Moreover, on fluoroscopy, retrograde peristalsis is seen. This transmits abnormal pressures up to the kidney, resulting in calyceal dilation out of proportion with the renal pelvic dilation. Histologic findings include an excess of circular muscle fibers and collagen in the distal ureter that may account for the problem (Tanagho et al, 1970). Some ultrastructural studies show that this obstruction is similar in appearance to obstruction of the ureteropelvic junction.

Currently, most cases are discovered on prenatal sonography. Sonography usually shows the pathognomonic configuration of a dilated distal ureter, a less dilated proximal ureter, a relatively normal-appearing renal pelvis, and calyces blunted out of proportion to the renal pelvis (Figure 37–12).

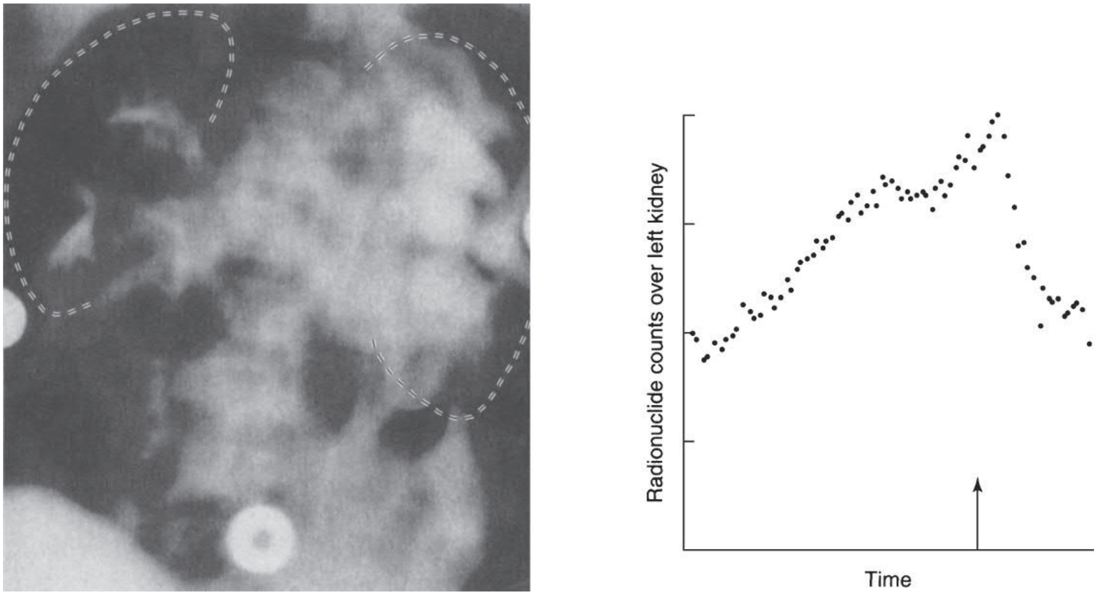
It was assumed previously that surgery was indicated in most cases. Ureteral reimplantation with excision of the distal ureter is curative. Because of the excessive dilation of the ureter, ureteral tapering or folding may be necessary (Ehrlich, 1985; Hanna, 1982; Hendren, 1969). Because the ureteral muscle is generally healthy, these cases have an excellent prognosis. Interestingly, there are some less invasive surgical options, although they are not commonly employed (Kaefer, 2017). More important, it has become obvious that most patients will undergo spontaneous resolution or at least stabilize. A period of observation is nearly always appropriate when the diagnosis is made in an asymptomatic patient Baskin et al, 1994; Chertin et al, 2008). Because of the high risk of infection, 1–2 years of prophylactic antibiotics are recommended in neonates. Ultimately, few of these cases require operative intervention.



▲ **Figure 37–12.** Obstructed megaureter. Follow-up study in a 9-month-old boy with unilateral hydronephrosis detected by ultrasonography in utero. Excretory urogram shows the classic configuration of a dilated distal ureter, a less dilated proximal ureter, and blunted calyces.

UPPER URINARY TRACT DILATATION WITHOUT OBSTRUCTION

It should not be assumed that every dilated upper urinary tract is obstructed. For example, reflux can cause hydronephrosis on ultrasound. Other cases in which the diagnosis of obstruction may be difficult include residual dilatation in a previously obstructed system, dilatation associated with bacterial infection (presumably related to a direct effect of endotoxin on the ureteral musculature), neonatal hydronephrosis, and prolonged polyuria in patients with diabetes insipidus.



▲ **Figure 37–13.** Upper urinary tract dilatation. ***Left:*** Three months after resection of posterior urethral valves, hydronephrosis in the right kidney has completely resolved. The left collecting system remains dilated. (*Dashed lines* outline kidneys.) ***Right:*** Radionuclide diuretic renography was performed to determine whether there was secondary ureteropelvic or ureterovesical obstruction. Renogram demonstrates clear-cut "washout" of radionuclide following injection of furosemide (*arrow*). There is no significant obstruction.

In such cases, the usual investigations may not provide enough information. A radionuclide diuretic renogram is especially helpful in distinguishing nonobstructive from obstructive dilation and in determining whether renal functional injury has occurred (Figure 37–13) (Thrall et al, 1981). However, the procedure must be performed carefully, as technical problems may confuse the results (Gungor et al, 2002; Nguyen et al, 1997). Use of percutaneous renal puncture is occasionally beneficial; in the dilated system, it carries minimal risk, making antegrade urography and pressure–flow studies feasible in selected cases. Measurement of the renal pelvic pressure during infusion of saline into the renal pelvis at high rates (10 mL/min) (the **Whitaker test**) may help differentiate nonobstructive from obstructive dilation (Wolk and Whitaker, 1982). Unfortunately, there is no true gold standard, and these studies do not always agree; clinical judgment is the final arbiter.

ACQUIRED DISEASES OF THE URETER

Nearly all acquired diseases of the ureter are obstructive in nature. Although they are seen frequently, their actual incidence is unknown. Their clinical manifestations, effects on the kidney, complications, and treatment are similar to those described previously. The lesions can be broadly categorized as either intrinsic or extrinsic.

A. Intrinsic Ureteral Obstruction

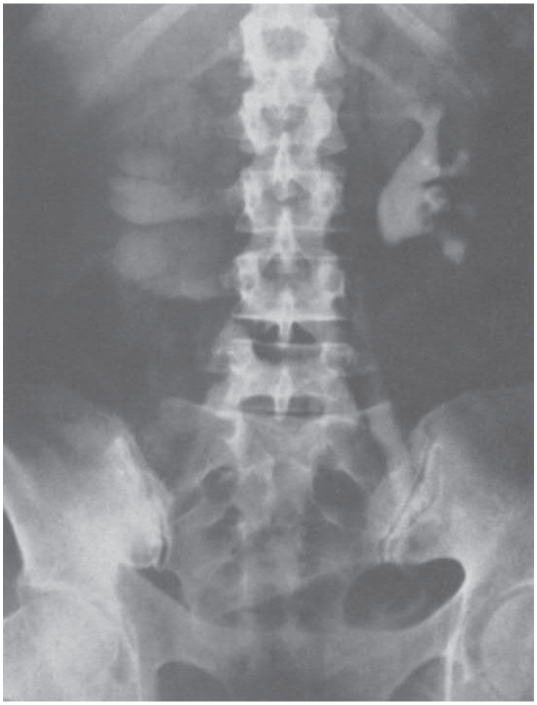
The most common causes of intrinsic ureteral obstruction are as follows:

1. Ureteral stones (see Chapter 17)
2. Transitional cell tumors of the ureter (see Chapter 22)
3. Chronic inflammatory changes of the ureteral wall (usually due to tuberculosis or schistosomiasis) leading to contracture or insufficient peristalsis (see Chapter 15 and Figures 15-2 and 15-4)

B. Extrinsic Ureteral Obstruction

The most frequent causes of extrinsic ureteral obstruction are as follows:

1. Severe constipation, sometimes with bladder obstruction, seen primarily in children but in adult women as well.
2. Secondary obstruction due to kinks or fibrosis around redundant ureters. The primary process is either distal obstruction or massive reflux.
3. Benign gynecologic disorders such as endometriosis or right ovarian vein syndrome.
4. Local neoplastic infiltration associated with carcinoma of the cervix, bladder, or prostate.
5. Pelvic lymphadenopathy associated with metastatic tumors.

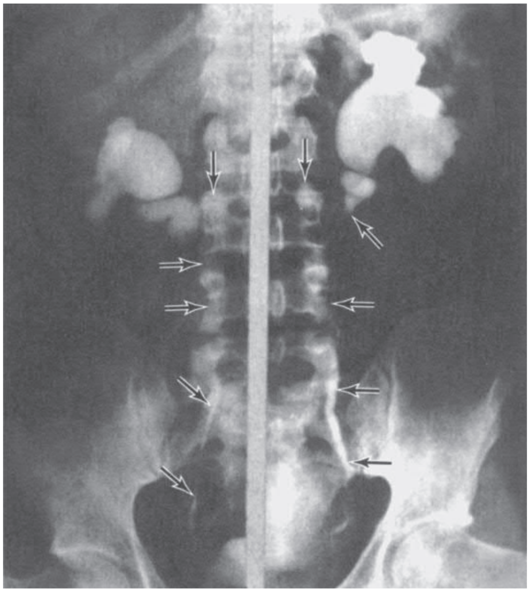


▲ **Figure 37–14.** Ureteral obstruction. Excretory urogram obtained 2 weeks after a radical hysterectomy shows bilateral ureteral obstruction and marked hydronephrosis on right.

6. Iatrogenic ureteral injuries, primarily after extensive pelvic surgery (Figure 37–14) and after extensive radiotherapy.
7. Retroperitoneal fibrosis.

RETROPERITONEAL FIBROSIS (RETROPERITONEAL FASCIITIS, CHRONIC RETROPERITONEAL FIBROPLASIA, ORMOND DISEASE)

One or both ureters may be compressed by a chronic inflammatory process that involves the retroperitoneal tissues over the lower lumbar vertebrae. There are numerous causes of retroperitoneal fibrosis. Malignant diseases (most commonly Hodgkin's disease, carcinoma of the breast, and carcinoma of the colon) should always be suspected and ruled out. Some medications have been implicated, most notably methysergide (Sansert), an ergot derivative used to treat migraine headaches. Rarely, membranous glomerulonephritis (Shirota et al, 2002), inflammatory bowel disease (Siminovitch and Fazio, 1980), or an aortic aneurysm (Brock and Soloway, 1980) are responsible. The remainder of cases are idiopathic, a condition sometimes referred to as **Ormond disease**. It has most recently been assumed to be autoimmune, and in men especially, IgG4 is likely involved (Zen et al, 2009).



▲ **Figure 37–15.** Retroperitoneal fibrosis. Right and left kidneys of same patient as shown by excretory urography. Note medial marked obstruction. (Used with permission from JA Hutch.)

The symptoms are nonspecific and include low back pain, malaise, anorexia, weight loss, and, in severe cases, uremia (Swartz, 2009). Infection is uncommon. The diagnosis is usually made by computed tomography (CT) scan, and the coronal images are pathognomonic (Figure 37–15). There is medial deviation of the ureters with proximal dilation. A long segment of ureter is usually involved, and there is a pipestem appearance caused by aperistalsis related to the fibrosis. Ultrasonography is useful for monitoring the response to therapy. CT scanning or magnetic resonance imaging is essential for evaluating the retroperitoneum itself, in addition to imaging the ureters (Hricak et al, 1983). Recently, positron emission tomography scanning has been advocated to diagnose metastatic cancer and to follow the severity of the inflammatory lesions (Piccoli, 2010).

Spontaneous regression has been reported (Kune and Kitamura, 2001; Yamakawa et al, 2001); however, treatment is usually surgical. A course of corticosteroids may be successful, but recurrence is high if not continued (Swartz, 2009). When the response to corticosteroids is poor or the obstruction is severe, the ureter must be dissected surgically from the fibrous plaque. After it is freed, it should either be placed intraperitoneally or wrapped in omentum in an attempt to prevent recurrence; this procedure can also be performed laparoscopically (Stein et al, 2010). A more recent study has suggested that earlier surgery is better (O'Brien and Fernando, 2017). Numerous biopsies of the fibrous tissue should be obtained at the time of operation to determine whether there is a malignant tumor.

URETERAL OBSTRUCTION SECONDARY TO MALIGNANT DISEASE

Ureteral obstruction associated with widespread malignant disease was at one time a terminal event. Because therapy for malignant diseases has improved, urinary diversion is indicated more frequently in such cases. Diversion usually is necessary for relatively short periods of time; either the tumor is progressive, or if therapy is effective, the obstruction resolves. Thus, the goal of treatment is to leave the urinary tract intact and effect as little morbidity as possible. This can be accomplished with indwelling stents passed either retrograde during cystoscopy or antegrade using percutaneous techniques.

BIBLIOGRAPHY

Amar AD: Ureteropyelostomy for relief of single ureteral obstruction due to retroperitoneal fibrosis in a patient with ureteral duplication. J Urol 1970;103:296–297.

Anderson JC: Hydronephrosis. Heinemann, 1963.

Bagheri F, et al: Laparoscopic repair of circumcaval ureter: One-year follow-up of three patients and literature review. Urology 2009;**74**:148–153.

Baskin LS, et al: Primary dilated megaureter: Long-term followup. J Urol 1994;152:618–621.

Belman AB, et al: Surgical management of duplication of the collecting system. J Urol 1974;112:316–321.

Brock J, et al: Retroperitoneal fibrosis and aortic aneurysm. Urology 1980;15:14–16.

Capello SA, et al: Prenatal ultrasound has led to earlier detection and repair of ureteropelvic junction obstruction. J Urol 2005;174:1425–1428.

Capello SA, et al: Prenatal ultrasound has led to earlier detection and repair of ureteropelvic junction obstruction. J Urol 2005;174:1425–1428.

Chan YY, et al: Outcomes after pediatric open, laparoscopic, and robotic pyeloplasty at academic institutions. J Pediatr Urol 2017;13:49, e1–e6.

Chertin B, et al: Long-term follow up of antenatally diagnosed megaureters. J Pediatr Urol 2008;4:188–191.

Culp OS, et al: A pelvic flap operation for certain types of ureteropelvic obstruction: Preliminary report. Mayo Clin Proc 1951;26:483–488.

Davis DM: Intubated ureterotomy: A new operation for ureteral and ureteropelvic strictures. Surg Gynecol Obstet 1943;513.

Drube J, et al: Urinary proteome analysis identifies infants but not older children requiring pyeloplasty. Pediatr Nephrol 2010;25:1673–1678.

Ehrlich RM: The ureteral folding technique for megaureter surgery. J Urol 1985;134:668–670.

Foley FEB: A new plastic operation for stricture at the ureteropelvic junction. J Urol 1937:643.

Glassberg KI, et al: Suggested terminology for duplex systems, ectopic ureters and ureteroceles. J Urol 1984;132:1153–1154.

Gungor F, et al: Effect of the size of regions of interest on the estimation of differential renal function in children with congenital hydronephrosis. Nucl Med Commun 2002;23:147–151.

Hanna MK, et al: Ureteral structure and ultrastructure. Part II. Congenital ureteropelvic junction obstruction and primary obstructive megaureter. J Urol 1976;116:725–730.

Hanna MK: Recent advances and further experience with surgical techniques for one-stage total remodeling of massively dilated ureters. Urology 1982;19:495–504.

Hendren WH: Operative repair of megaureter in children. J Urol 1969;101:491–507.

How GY, et al: Neuronal defects an etiological factor in congenital pelviureteric junction obstruction? J Pediatr Urol 2018;14(1).

Howe A, et al: Robotic surgery in pediatric urology. Asian J Urol 2017;4:55–67.

Hricak H, et al: Nuclear magnetic resonance imaging in retroperitoneal fibrosis. Am J Roentgenol 1983;141:35–38.

Jacobs BL, et al: The comparative effectiveness of treatments for ureteropelvic junction obstruction. Urology 2018;111:72–77.

Johnston JH, et al: Pelvic hydronephrosis in children: A review of 219 personal cases. J Urol 1977;117:97–101.

Johnston JH: The pathogenesis of hydronephrosis in children. Br J Urol 1969;41:724–734.

Kaefer M: Unconventional surgical strategies for the obstructed megaureter-what are the options and when should we use them? J Urol 2017;198:995–996.

Kaya C, et al: Extracellular matrix degradation and reduced neural density in children with intrinsic ureteropelvic junction obstruction. Urology 2010;76:185–189.

Kern AJM, et al: Simple visual review of pre- to post-operative renal ultrasound images predicts pyeloplasty success equally as well as geometric measurements: A blinded comparison with a gold standard. J Pediatr Urol 2017;13:401, e1–e7.

Koff SA, et al: Pathophysiology of ureteropelvic junction obstruction: Experimental and clinical observations. J Urol 1986;136:336–338.

Kume H, et al: Spontaneous regression of bilateral hydronephrosis due to retroperitoneal fibrosis. Scand J Urol Nephrol 2001;35:255–256.

Lipson JA, Coakley FV, Baskin LS, Yeh BM: Subtle renal duplication as an unrecognized cause of childhood incontinence: Diagnosis by magnetic resonance urography. J Pediatr Urol 2008;4:398–400.

Lopes RI, et al: Clinical outcomes of the upper urinary tract after ureteral clipping for treatment of low functioning or nonfunctioning renal moieties. J Urol 2018;199:558–564.

Mendelsohn C, et al: Using mouse models to understand normal and abnormal urogenital tract development. Organogenesis 2009;5:306–314.

Nagalakshmi VK, et al: The ureteric bud epithelium: Morphogenesis and roles in metanephric kidney patterning. Mol Reprod Dev 2015;**82**:151–166.

Nation EF: Duplication of the kidney and ureter: A statistical study of 230 new cases. J Urol 1944;51:456–465.

Nguyen HT, Gluckman GR, Kogan BA: Changing the technique of background subtraction alters calculated renal function on pediatric mercaptoacetyltriglycine renography. J Urol 1997;158:1252–1256.

O'Brien T, Fernando A: Contemporary role of ureterolysis in retroperitoneal fibrosis: Treatment of last resort or first intent? An analysis of 50 cases. BJU Int 2017;120:556–561.

Onal B, Kogan BA: Natural history of patients with multicystic dysplastic kidney - what followup is needed? J Urol 2006;176: 1607–1611.

Piccoli GB, Consiglio V, Arena V, et al: Positron emission tomography as a tool for the 'tailored' management of retroperitoneal fibrosis: A nephro-urological experience. Nephrol Dialysis Transplant 2010;25:2603–2610.

Shirota S, Tsuchiya K, Takada M, et al: Retroperitoneal fibrosis associated with membranous nephropathy effectively treated with steroids. Intern Med 2002;41:20–25.

Siminovitch JM, Fazio VW: Ureteral obstruction secondary to Crohn's disease: A need for ureterolysis? Am J Surg 1980;139:95–98.

Smart WR: Surgical correction of hydronephrosis. Campbell's Urol 1979:3.

Smith KE, Holmes N, Lieb JI, et al: Stented versus nonstented pediatric pyeloplasty: A modern series and review of the literature. J Urol 2002;168:1127–1130.

Snyder HM, Johnston JH: Orthotopic ureteroceles in children. J Urol 1978;119:543–546.

Stein RJ, Patel NS, Quinn K, et al: Laparoscopic ureterolysis with omental wrap for idiopathic retroperitoneal fibrosis. BJU Int 2010;106:703–707.

Swartz RD: Idiopathic retroperitoneal fibrosis: A review of the pathogenesis and approaches to treatment. Am J Kidney Dis 2009;54:546–553.

Tanagho EA, Smith DR, Guthrie TH: Pathophysiology of functional ureteral obstruction. J Urol 1970;104:73–88.

Tanagho EA: Embryologic basis for lower ureteral anomalies: A hypothesis. Urology 1976; 7:451–464.

Thrall JH, Koff SA, Keyes JW Jr: Diuretic radionuclide renography and scintigraphy in the differential diagnosis of hydroureteronephrosis. Semin Nucl Med 1981;11:89–104.

Wang MH, Greenfield SP, Williot P, Rutkowski J: Ectopic ureteroceles in duplex systems: Long-term follow up and "treatment-free" status. J Pediatr Urol 2008;**4**:183–187.

Whitaker RH: Methods of assessing obstruction in dilated ureters. Br J Urol 1973; 45:15–22.

Wolk FN, Whitaker RH: Late followup of dynamic evaluation of upper urinary tract obstruction. J Urol 1982;128:346–347.

Yamakawa H, Sekine A, Yamanaka Y, et al: Pathologically proven spontaneous remission of IgG4-related retroperitoneal fibrosis. Intern Med 2017;56:1867–1871.

Zen Y, Onodera M, Inoue D, et al: Retroperitoneal fibrosis: A clinicopathologic study with respect to immunoglobulin G4. Am J Surg Pathol 2009;33:1833–1839.

This page intentionally left blank

38

Disorders of the Bladder, Prostate, and Seminal Vesicles

Samuel L. Washington III, MD; & Katsuto Shinohara, MD

CONGENITAL ANOMALIES OF THE BLADDER

Exstrophy

Exstrophy of the bladder is a rare congenital anomaly with complete ventral defect of the urogenital sinus and the overlying skeletal system (Gambhir et al, 2008). Incidence of this anomaly is reported to be 3.3 per 100,000 births. The male-to-female ratio is about 1.6 (ICBDMS, 1987; Jayachandran et al, 2011; Feldkamp et al, 2011).

A. Signs and Symptoms

The lower central abdomen is occupied by the inner surface of the posterior wall of the bladder, whose mucosal edges are fused with the skin. Urine empties onto the abdominal wall from the ureteral orifices.

The rami of the pubic bones are widely separated. The pelvic ring thus lacks rigidity, the femurs are rotated externally, and the child "waddles like a duck."

The rectus muscles are widely separated from each other caudally. A hernia, made up of the exstrophic bladder and surrounding skin, is present.

Epispadias is almost always associated. Undescended testicles may be seen, and the anus and vagina are located anteriorly. Urinary tract infection and hydronephrosis are common.

B. Diagnosis

Prenatal diagnosis is difficult, with approximately 13–16% that can be identified prenatally on routine ultrasound (Jayachandran et al, 2011; Austin et al, 1998; Emanuel et al, 1995; Cervellione et al, 2015). Up to 6% of babies will present with other congenital abnormalities (Cervellione et al, 2015) such as exposed bladder mucosa seen at time of birth or separation of pubic bones seen on x-ray.

C. Treatment

Historical treatment includes staged repair of this anomaly (Stec et al, 2012). The first stage consists in closing the abdominal wall, the bladder, and the posterior urethra. An orthopedic procedure of sacral osteotomy in order to close the abdominal wall may be necessary (Meldrum et al, 2003; Suson et al, 2013; Vining et al, 2011). Mollard et al (1994) recommend the following steps for satisfactory repair of bladder exstrophy (Mollard et al, 1993): (1) bladder closure with sacral osteotomy in order to close the pelvic ring at the pubic symphysis (Cervellione, 2011), plus lengthening of the penis; (2) antiureteral reflux procedure and bladder neck reconstruction; and (3) repair of the epispadiac penis. Treatment needs to be initiated prior to the fibrosis of the bladder mucosa in order to repair this anomaly completely (Oesterling and Jeffs, 1987). When the bladder is small, fibrotic, and inelastic, functional closure becomes inadvisable, and urinary diversion with cystectomy is the treatment of choice. The modern approach is to perform primary repair of this anomaly completely, although some may opt to delay treatment for 2–3 months after birth rather than begin it within 72 hours of birth, as had been done traditionally (Mitchell, 2005; Mourtzinos and Borer, 2004).

D. Prognosis

Common complications after surgical repair have been described in the literature (Gargallo et al, 2011; Light and Scott, 1983; Perlmutter et al, 1991; Gargallo and Borer, 2007). Complete primary closure appears to be the best choice for improved continence. Previous studies show better outcomes with primary repair (Grady et al, 1999; Kiddoo et al, 2004; Lowentritt et al, 2005), while more recent studies with longer-term follow-up (up to 20 years) demonstrate that approximately half report having dry intervals between voiding lasting at least three hours and/or with no complaints of urinary leakage (Gupta et al, 2014; Taskinen and Suominen, 2013). Adenocarcinoma of the bladder and rectum are noted to be in higher frequency (Husmann and Rathbun, 2008).

Persistent Urachus

Embryologically, the allantois connects the urogenital sinus with the umbilicus. Normally, the allantois is obliterated and is represented by a fibrous cord (urachus) extending from the dome of the bladder to the navel (Bauer and Retik, 1978). Urachal formation is directly related to bladder descent. Lack of descent is more commonly associated with patent urachus than with bladder outlet obstruction (Scheye et al, 1994).

A. Sign and Symptoms

If the urachal obliteration is complete except at the superior end, a draining umbilical sinus may be noted. If it becomes infected, the drainage will be purulent. If the inferior end remains open, it will communicate with the bladder, but this does not usually produce symptoms. Rarely, the entire tract remains patent, in which case urine drains constantly from the umbilicus. This is apt to become obvious within a few days of birth. If only the ends of the urachus seal off, a cyst of that body may form and may become quite large, presenting a low midline mass (Figure 38–1) (al-Hindawi and Aman, 1992). If the cyst becomes infected, signs of general and local sepsis will develop (Mesrobian et al, 1997).

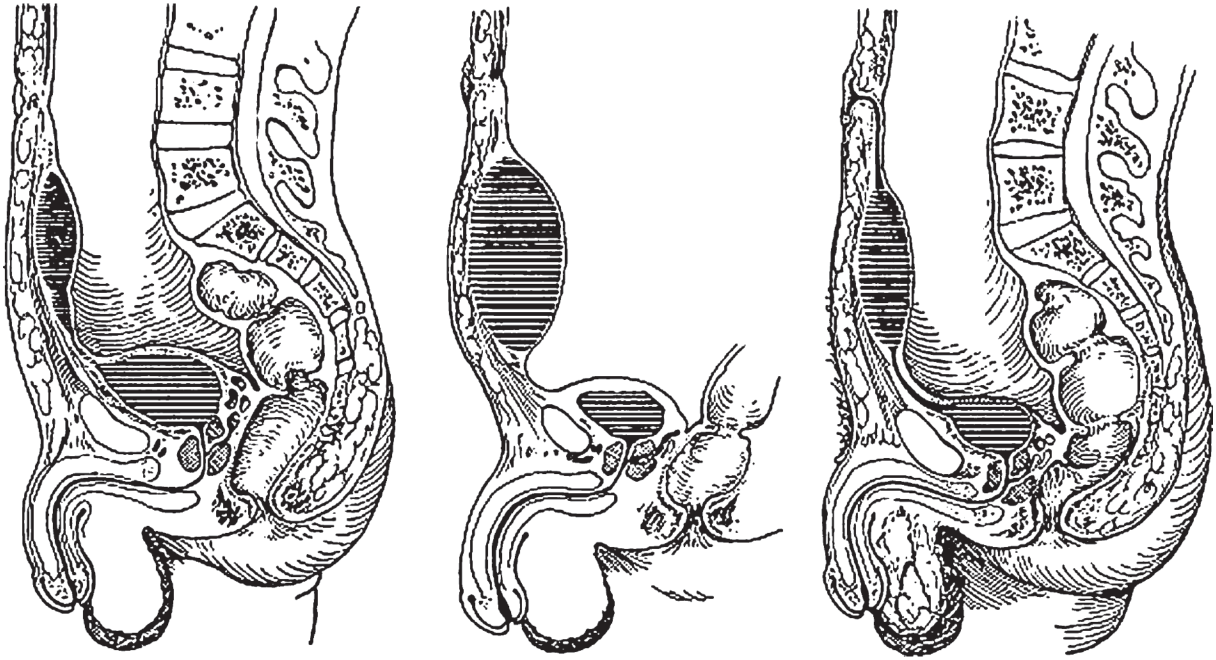
Adenocarcinoma may occur in an urachal cyst, particularly at its vesical extremity (Figure 38–2), and tends to invade the tissues beneath the anterior abdominal wall.

B. Diagnosis

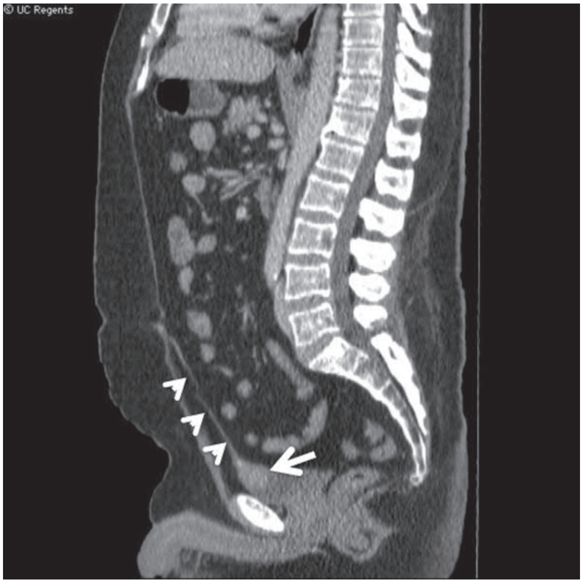
Physical examination reveals an opening sinus or lower abdominal mass. Computed tomography (CT) scan, magnetic resonance imaging (MRI), or ultrasound may show cystic structure adjacent to the bladder dome (Chouhan et al, 2010; Cilento et al, 1998; Holten et al, 1996). Cystoscopic examination may show extrinsic compression from the mass. Stones may develop in a cyst of the urachus and can be identified on a plain x-ray film.

C. Treatment

Treatment consists in excision of the urachus, which lies on the peritoneal surface (Chan et al, 2009; Destri et al, 2011; Yohannes et al, 2004; Stone et al, 1995). If adenocarcinoma is present, radical resection is required. Unless other serious congenital anomalies are present, the prognosis is good (Upadhyay and Kukkady, 2004). The complication of adenocarcinoma offers a poor prognosis (Gopalan, 2009).



▲ **Figure 38–1.** Diagrams showing various types of patent urachus. ***Left:*** Complete atresia toward umbilicus but patent toward bladder. ***Center:*** Atresia on both ends leading cystic dilation in the middle. ***Right:*** Completely patent urachus with cystic dilation.



▲ **Figure 38–2.** MRI midline sagittal view of a case with adenocarcinoma of the urachus. A cordlike urachus is seen connecting the bladder dome and umbilicus (*arrow heads*). A soft-tissue mass is seen in the dome of the bladder (*arrow*). (Used with permission from Dr. Fergus Coakley.)

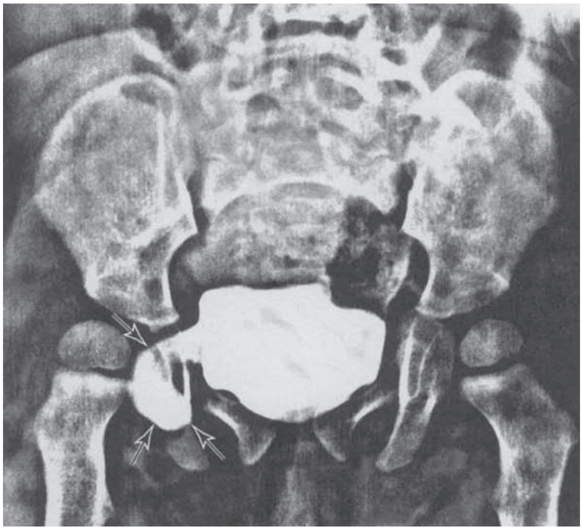
Other Bladder Anomalies

A. Diverticulum

Congenital diverticulum is found in approximately 1.7% of children (Blane et al, 1994). This is caused by the congenital weakness of the Waldeyer fascial sheath. Most of the cases are asymptomatic; however, a diverticulum can cause urinary tract infection, and in rare cases, it can cause ureteral or bladder outlet obstruction (Bhat et al, 2012; Pieretti and Pieretti-Vanmarcke, 1999; Bogdanos et al, 2005).

B. Bladder Ears

One side of the bladder may become involved in an inguinal hernia (Figure 38–3). Such a mass may recede on urination. The condition can be found during x-ray contrast studies of the urinary tract (Bjurlin et al, 2018; Catalano, 1997). However, it is more commonly found as a previously unsuspected complication during surgical correction of a hernia (McCormick et al, 2005; Patle et al, 2011).



▲ **Figure 38–3.** Cystogram demonstrating sliding hernia of the bladder in the inguinal canal (*arrows*).

C. Megacystis

Megacystis is a condition with enlarged bladder due to overdistention during development, commonly associated with massive reflux with hydronephrosis (Burbige et al, 1984). It can be identified prenatally by ultrasound, found in 1 out of 1500 pregnancies in the first trimester (Sebire et al, 1996). This condition can be associated with other conditions, such as posterior valve abnormalities (Confer et al, 2010), Ehlers–Danlos syndrome (Sato, 1993), and meningomyelocele (Blane et al, 1994). Spontaneous resolution has been reported in up to 20% of cases and gestational age at time of resolution has been shown to be predictive of later complications (Fontanella et al, 2017).

ACQUIRED DISEASES OF THE BLADDER

Interstitial Cystitis or Bladder Pain Syndrome

Interstitial cystitis/bladder pain syndrome is an unknown etiology syndrome characterized by urinary frequency, urgency, and bladder pain (Nickel, 2004). In the past, it was reported to frequently affect middle-aged women; however, studies revealed that it affects men and women in all age groups (Kusek and Nyberg, 2001). Recent survey-based studies found interstitial cystitis/bladder pain syndrome prevalent in 1.9–4.2% of adult men (Suskind et al, 2013) and 2.7–6.5% of adult women (Berry et al, 2011).

A. Sign and Symptoms

Common symptoms with IC/BPS are bladder pain worsened with bladder filling, reaction to certain food intake, and burning on urination. Urinary frequency, nocturia, and urgency are also common. Although the exact definition varies between national and international guidelines, pain often described as pressure or discomfort remains the hallmark symptom.

B. Etiology

The etiology of IC/BPS is unknown, and various causes are proposed. These include increased mast cell in the bladder wall, deficiency of glycosaminoglycan layer over bladder mucosa leading to bladder wall inflammation by urine stimulation, unknown virus infection, toxic substances in the urine, and autoimmune disorder (Buffington, 2004; Burkman, 2004; Clemens et al, 2008; Elbadawi, 1997; Wesselmann, 2001).

C. Diagnosis

The basic assessment of a patient suspected to have interstitial cystitis/bladder pain syndrome requires taking a thorough history with ascertainment of the degree of baseline symptoms and pain, performing a focused physical exam, and consideration of additional diagnostic studies such as laboratory testing or procedures to rule out other potential etiologies. Guidelines published by the American Urological Association recommend that the initial evaluation include postvoid residual volume measurements; urine studies such as cytology, urinalysis, and urine culture; self-reported questionnaires, and pain-level evaluation (for men with suspected bladder pain syndrome, reported pain with ejaculation or urination may be more consistent with chronic prostatitis and may require further investigation):

1. **National Institute of Diabetes and Digestive and Kidney Disease criteria**—Since IC/BPS is an unknown-etiology clinical symptom complex, National Institute of Diabetes and Digestive and Kidney Disease criteria were created to rule in/out this diagnosis (Gillenwater and Wein, 1988; Nordling, 2004; Oberpenning et al, 2002) (Table 38–1).
2. **Validated questionnaires**—The Wisconsin Interstitial Cystitis Scale and The Interstitial Cystitis symptom and Problem Index (O'Leary et al, 1997) are validated questionnaires and useful in diagnosis and evaluation of treatment effectiveness (Sirinian et al, 2005).
3. **Laboratory tests**—The urine is almost always free of infection. Microscopic hematuria may be noted. Results of renal function tests are normal except in the occasional patient in whom vesical fibrosis has led to vesicoureteral reflux or obstruction. No urine cytology or markers are found to be specific to IC/BPS (Hurst et al, 1993). No serologic tests are shown to be diagnostic for this condition.
4. **Imaging**—No radiographic findings are found to be specific to IC/BPS. Excretory urograms are usually normal unless reflux has occurred, in which case hydronephrosis is found. The accompanying cystogram reveals a bladder of small capacity; reflux into a dilated upper tract may be noted on cystography.
5. **Urodynamic studies**—Urodynamic studies are not required for diagnosis of IC/BPS; however, they can be used to rule out other conditions, such as neurogenic bladder or bladder outlet obstruction.

Table 38–1. National Institute of Diabetes and Digestive and Kidney Disease criteria for interstitial cystitis.

To be diagnosed with interstitial cystitis, patients must have either
    Glomerulations on cystoscopic examination or a classic Hunner's ulcer
And either
    Pain associated with the bladder or urinary urgency
An examination for glomerulations should be undertaken after distention of the bladder under anesthesia to 80–100 cm of water pressure for 1–2 minutes
The bladder may be distended up to two times before evaluation
The glomerulations must
    Be diffuse—present in at least 3 quadrants of the bladder
    Be present at a rate of at least 10 glomerulations per quadrant
    Not be along the path of the cystoscope (to eliminate artifact from contact instrumentation)
The presence of any one of the following criteria excludes the diagnosis of interstitial cystitis:

1. Bladder capacity of >350 cc on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100 cc of gas or 150 cc of water during cystometry, using a fill rate of 30–100 cc/min
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described above
4. Duration of symptoms <9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics
7. A frequency of urination, while awake, of less than eight times per day
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period
9. Bladder or ureteral calculi
10. Active genital herpes
11. Uterine, cervical, vaginal, or urethral cancer
12. Urethral diverticulum
13. Cyclophosphamide or any type of chemical cystitis
14. Tuberculous cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumors
17. Vaginitis
18. Younger than 18 years

6. **Cystoscopy**—Cystoscopy is not required in order to make a diagnosis of IC/BPS but may be used when the diagnosis is suspected. Diagnostic cystoscopy is commonly performed under anesthesia in order to adequately distend the bladder. Typical cystoscopic findings associated with IC/BPS are reduced capacity, scarring and cracking of the mucosa with distention (Hunner's ulcer), and appearance of glomerulation (diffuse petechial hemorrhages in the mucosa) after distension. However, the classic presentation of a Hunner's ulcer is rare. Glomerulation can be seen with other conditions, and the finding is not specific to IC/BPS (Ottem and Teichman, 2005; Simon et al, 1997). These findings also

do not exclude a diagnosis of IC/BPS but may offer potential additional etiologies of the presenting symptoms.

7. **Histology**—Bladder biopsy has shown increased numbers of mast cells in the bladder wall (Sant et al, 2003). However, this finding does not include or exclude the diagnosis (Johansson and Fall, 1990).
8. **KCl test**—Patients with deficiency of the urothelial defense layer (Nickel et al, 1993) may experience severe pain with instillation of potassium chloride solution in the bladder. However, this test is controversial and not widely used.

D. Differential Diagnosis

Tuberculosis of the bladder may cause true ulceration but is most apt to involve the region of the ureteral orifice that drains the tuberculous kidney. Vesical ulcers due to schistosomiasis cause symptoms similar to those of interstitial cystitis. The diagnosis is suggested if the patient lives in an area in which schistosomiasis is endemic. Nonspecific vesical infection seldom causes ulceration. Pus and bacteria are found in the urine. Antimicrobial treatment is effective.

E. Treatment

While treatment regimens may vary, the AUA amended treatment guidelines in 2014, providing a stepwise algorithm for treatment of patient with IC/BPS.

First-line treatment options include stress management/general relaxation techniques, pain management, patient education, and self-care/behavioral modifications. Second-line therapy options include oral medications, intravesical instillations, and pain management. Other options are as follows:

1. **Oral medication**—Amitriptyline has shown to improve IC/BPS symptoms including pain and urgency intensity (van Ophoven et al, 2004). A multicenter double-blinded, randomized controlled trial showed that treatment-naive patients may have limited benefit from amitriptyline combined with education and behavioral modification, thus supporting its use as a second-line treatment option (Foster et al, 2010). Cimetidine, an H_2-receptor antagonist, has been shown to improve symptoms such as suprapubic pain and nocturia in a prospective, randomized, double-blind placebo-controlled trial (Thilagarajah et al, 2001). Hydroxyzine has also been evaluated as second-line therapy in the treatment of IC/PBS (Sant et al, 2003; Theoharides, 1994). Pentosan polysulfate provides a protective coating in the bladder and supposedly reduces IC/BPS-related pain (Parsons and Mulholland, 1987). However, a randomized study has shown no significant benefit of the medicine over placebo (Nordling, 2004; Sant et al, 2003; Sairanen et al, 2005). Cyclosporine A has been shown to be more effective than pentosan polysulfate; however, its toxicity limits its usage (Sairanen et al, 2005). Anticholinergics are frequently used to control frequency and urgency.
2. **Other therapy**—Other nonspecific medications, such as analgesics, anti-inflammatory agents, gabapentin, and serotonin reuptake inhibitors, can be used. Transcutaneous electrical nerve stimulation (Comiter, 2003) and biofeedback therapy may have some benefit for controlling the symptoms (Peters et al, 2007). Diet modification to avoid certain foods or drinks may have a role in the treatment (Chaiken et al, 1993).
3. **Surgical therapy**—Surgical therapy is rarely indicated. Even after cystectomy, some patients continue to experience pain (Baskin and Tanagho, 1992). For those who have small bladder capacity, an augmentation procedure can be indicated. Trials of botulinum toxin A injection in the bladder wall have shown to improve symptoms and bladder capacity.

Therapies not to be offered include long-term antibiotic therapy, pelvic floor/Kegel exercises, intravesical BCG, and hydrodistension, and long-term systemic steroids based on the amended AUA guidelines.

F. Prognosis

Most patients respond to one of the conservative measures mentioned previously. IC/BPS is a chronic condition and requires patient understanding and support.

Foreign Body Inserted into the Bladder

Numerous objects have been found in the urethra and bladder of both men and women. Some of them find their way into the urethra in the course of inquisitive self-exploration (Cardozo, 1997; Mastromichalis et al, 2011). Other objects can migrate in the bladder through erosion. Reported objects found within the urinary tract include intrauterine contraceptive devices (Bjørnerem and Tollan, 1997; Chuang et al, 2010; Hick et al, 2004; Jin et al, 2016), metal screws (Brusky et al, 2008), and rubber tubes or catheters (Stamatiou and Moschouris, 2016; Grubišić et al, 2014). Other foreign bodies placed during surgery include hernia repair mesh (Bjurlin, 2011), drain, vaginal sling material, and bone fragments after trauma (Stone et al, 1995).

The presence of a foreign body causes cystitis. Hematuria is not uncommon. Embarrassment may cause the victim to delay medical consultation. A plain x-ray of the bladder area discloses metal objects. Nonopaque objects sometimes become coated with calcium. Cystoscopy visualizes them all.

Cystoscopic or suprapubic removal of the foreign body is indicated. If not removed, the foreign body may lead to infection of the bladder. If the infecting organisms are urea splitting, the alkaline urine (which causes increased insolubility of calcium salts) contributes to rapid formation of stone on the foreign object.

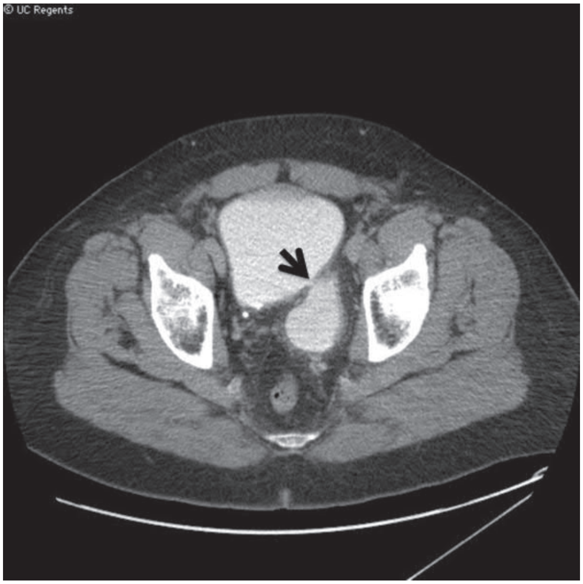
Vesical Manifestations of Allergy

So many mucous membranes are affected by allergens that the possibility of allergic manifestations involving the bladder must be considered. Hypersensitivity is occasionally suggested in cases of recurrent symptoms of acute "cystitis" in the absence of urinary infection or other demonstrable abnormality. During the attack, general erythema of the vesical mucosa may be observed and some edema of the ureteral orifices noted. Sometimes, lesions mimic malignancy (Salman et al, 2006; Thompson et al, 2005). Biopsy of the bladder wall reveals diffuse eosinophilic cell infiltrations (eosinophilic cystitis) (Popescu et al, 2009; Rubin and Pincus, 1974).

A careful history may reveal that these attacks follow the ingestion of a food not ordinarily eaten (eg, fresh lobster). Sensitivity to spermicidal creams is occasionally observed. If vesical allergy is suspected, it may be aborted by the subcutaneous injection of 0.5–1 mL of 1:1000 epinephrine. Control may also be afforded with the use of one of the antihistamines. Steroid therapy is effective for severe cases (Watanabe et al, 2009). Skin testing has been shown positive in some cases.

Diverticula

Most vesical diverticula are acquired and are secondary to obstruction distal to either the vesical neck or the upper motor neuron type of neurogenic bladder. Increased intravesical pressure causes vesical mucosa to insinuate itself between hypertrophied muscle bundles, so that a mucosal extravesical sac develops (Figure 38–4). Often this sac lies just superior to the ureter and causes vesicoureteral reflux. The diverticulum is devoid of muscle and therefore has no expulsive power; residual urine is the rule, and infection is perpetuated. If the diverticulum has a narrow opening that interferes with its emptying, transurethral resection of its neck will improve drainage. Carcinoma occasionally develops on its wall (Prakash et al, 2010; Fu and Adeniran, 2015; Gerridzen and Futter, 1982), highlighting the importance of inspection of the internal surface of the diverticulum. Lack of wall thickness in diverticula can cause a potential early invasion of tumor and can result in a poor prognosis (Yu et al, 1993). Bladder-preserving options include transurethral resection, diverticulectomy, and partial cystectomy for smaller, low-grade tumors, and radical cystectomy for larger or higher-grade tumors (Walker et al, 2014). Diverticulectomy can be successfully performed laparoscopically (Khonsari et al, 2004; Kural et al, 2009; Macejko et al, 2008). Endoscopic management of bladder outlet obstruction must be performed if a diverticulectomy is performed. For poor surgical candidates, there have been case reports of successful endoscopic management (Chandhoke and Ghoniem, 2015; Pham et al, 2016).



▲ Figure 38–4. CT scan of the pelvis with contrast depicting a large bladder diverticulum filled with contrast and its orifice (*arrow*). (Used with permission from Dr. Fergus Coakley.)

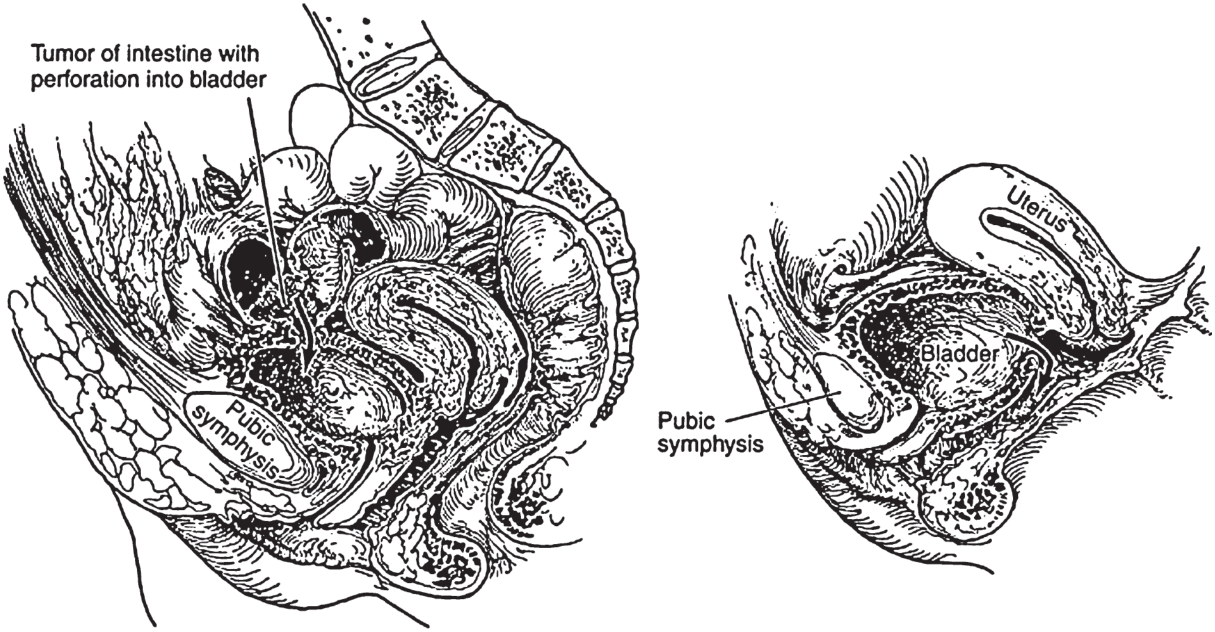
Vesical Fistulas

Vesical fistulas are common. The bladder may communicate with the skin, intestinal tract, or female reproductive organs (Figure 38–5). The primary disease is rarely urologic. The causes are as follows: (1) primary intestinal disease—diverticulitis, 50–60%; cancer of the colon, 20–25%; and Crohn's disease, 10% (Badlani et al, 1980; Simoneaux and Patrick, 1997); (2) primary gynecologic disease—pressure necrosis during difficult labor; advanced cancer of the cervix (Chapple et al, 1991; Gilour et al, 1999); (3) treatment for gynecologic disease following hysterectomy, low cesarean section, or radiotherapy for tumor (Ayhan et al, 1995); and (4) trauma. Ablative therapy of prostate cancer, such as cryosurgery or high-intensity focused ultrasound therapy, is a frequent cause of rectourethral fistula, but development of rectovesical fistula is rare.

Malignant tumors of the small or large bowel, uterus, or cervix may invade and perforate the bladder. Inflammations of adjacent organs may also erode through the vesical wall. Severe injuries involving the bladder may lead to perivesical abscess formation, and these abscesses may erode through the skin of the perineum or abdomen. The bladder may be inadvertently injured during gynecologic or intestinal surgery; cystotomy for stone or prostatectomy may lead to a persistent cutaneous fistula.

A. Sign and Symptoms

Symptoms arising from a vesicointestinal fistula include vesical irritability, the passage of debris (fecaluria) and gas through the urethra (pneumaturia), and usually a change in bowel habits (eg, constipation, abdominal distention, diarrhea) caused by primary intestinal disease (Kirsh et al, 1991). Signs of bowel obstruction may be elicited; abdominal tenderness may be found if the cause is inflammatory.



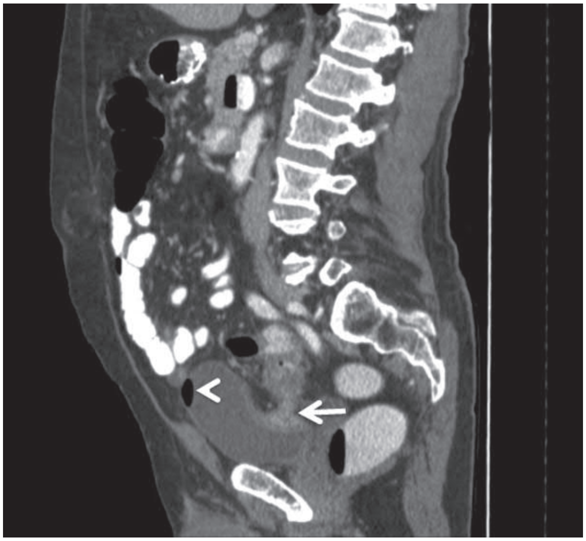
▲ **Figure 38–5.** Diagrams showing vesicoenteric fistula due to tumor in the sigmoid colon (***left***) and vesicovaginal fistula (***right***).

B. Laboratory Findings

Urinalysis shows increased WBC and RBC with bacteria. Urine cultures will commonly grow mixed bacterial flora.

C. Diagnosis

1. **Imaging studies**—CT scan and MRI are sensitive imaging modalities to detect enterovesical fistulae. It may show thickening of the bladder wall, mass adjacent to the bladder, and air in the bladder (Figure 38–6) (Moon et al, 2001). However, air in the bladder can be seen with an infection caused by gas-forming bacteria or instrumentation and is not solely diagnostic (Joseph et al, 1996). Barium enema is not sensitive enough to detect a fistula. However, it may show diverticulosis or malignancy. Cystography may show contrast in the bowel, although the sensitivity of cystography for identifying an enterovesical fistula tract is low. Radionuclide voiding cystography is reported to be sensitive test for enterovesical fistula diagnosis (Tamam et al, 2009).
2. **Cystoscopy**—Cystoscopic examination shows a severe localized inflammatory reaction from which bowel contents may exude. Catheterization of the fistulous tract may be feasible; the instillation of radiopaque fluid often establishes the diagnosis.



▲ **Figure 38–6.** CT scan of a case with vesicoenteric fistula due to diverticulitis demonstrating tissue thickening of the bladder wall with adhered sigmoid colon (*arrow*). Free air is seen in the bladder (*arrowhead*). (Used with permission from Dr. Fergus Coakley.)

3. **Other tests**—Tests using charcoal (Huettner et al, 1992) or poppy seeds Kwon et al, 2008) are employed to detect orally ingested charcoal or poppy seeds in patient urine. The Bourne test detects barium particles in urine after a barium enema (Amendola et al, 1984). Those tests may show the evidence of fistula; however, anatomical characterization cannot be achieved and these are mostly historical.

D. Differential Diagnosis

It is necessary to differentiate ureterovaginal from vesicovaginal fistula. The double-dye test can be used for this purpose. Phenazopyridine (Pyridium) is given by mouth to color the urine orange. One hour later, three cotton pledgets are inserted into the vagina, and methylene blue solution is instilled into the bladder. The patient is then told to walk around, after which the pledgets are examined. If the proximal cotton ball is wet or stained orange, the fistula is ureterovaginal. If the deep cotton pledget contains blue fluid, the diagnosis is vesicovaginal fistula. If only the distal pledget is blue, the patient probably has urinary incontinence (Raghavaiah, 1974).

E. Treatment

1. **Conservative management—**Fistula caused by Crohn's disease is commonly managed with medical therapy with steroid, sulfasalazine, and antibiotics. Patients who are poor surgical candidates with fistula from diverticulosis can be managed with antibiotics therapy.
2. **Surgical therapy**—Enterovesical fistula is commonly treated with the affected portion of bowel resection with or without bladder repair (Melchior et al, 2009). If inflammation by diverticulosis is severe, a staged approach with fecal diversion can be performed (Moss and Ryan, 1990). If malignancy is the cause of the fistula, partial or total cystectomy with affected bowel is necessary.

For vesicovaginal fistula, tiny openings may become sealed following the introduction of an electrode into the fistula to ablate mature tract epithelium. An indwelling catheter should be left in place for 2 weeks or more. Larger fistulas secondary to obstetric or surgical injuries respond readily to surgical repair, which may be done either through the vagina or transvesically (Huang et al, 2002; McKay, 2004). Persky and coworkers advised repairing such fistulas immediately rather than waiting for 3–6 months as counseled by most surgeons (Persky et al, 1979; Blaivas et al, 1995). Fistulas that develop following radiation therapy for cancer of the cervix are much more difficult to close because of the avascularity of the tissues. Surgical closure of fistulas that arise from direct invasion of the bladder by cervical carcinoma is impossible; diversion of the urinary stream above the level of the bladder (eg, ureterosigmoidostomy) is therefore necessary.

F. Prognosis

The surgical repair of fistulas caused by benign disease or operative trauma is highly successful. Postirradiation necrosis offers a more guarded prognosis. Fistulas secondary to invading cancers present difficult problems.

Pelvic Lipomatosis

The cause of pelvic lipomatosis is not known. The disorder seems to affect principally black men in the 20–40-year age group with hypertension (Heyns et al, 1991). There are no pathognomonic symptoms. There may be some dysuria or mild urinary obstructive symptoms. Examination may demonstrate microscopic hematuria, or a distended or enlarged pear-shaped bladder. Excretory urograms and cystography may show dilatation of both upper tracts and an upward displacement and lateral compression of the bladder (Miglani et al, 2010; Mordkin et al, 1997). In the perivesical area, x-ray reveals areas of radiolucency compatible with fatty tissue. A barium x-ray may show extrinsic pressure on the rectosigmoid. CT scan in association with the preceding findings establishes the diagnosis by clearly demonstrating the fatty nature of the perivesical tissue. Ultrasonography may be equally helpful. Cystitis glandularis is frequently associated with pelvic lipomatosis (Heyns et al, 1991; Masumori and Tsukamoto, 1999). Adenocarcinoma of the bladder can develop in the bladder in this condition (Sözen et al, 2004).

Noninfectious Hemorrhagic Cystitis

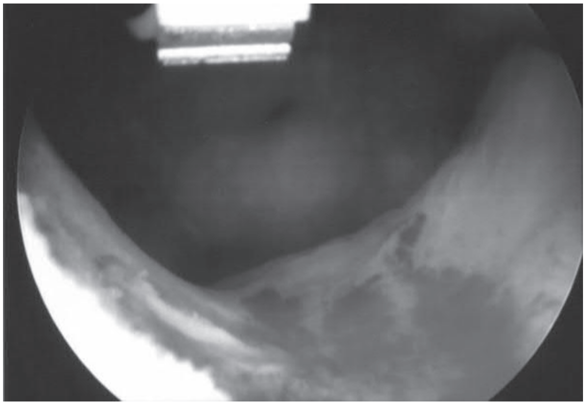
Some patients, following radiotherapy for carcinoma of the cervix, bladder, or prostate, are prone to intermittent, often serious vesical hemorrhage. The same is true of those given cyclophosphamide or ifosfamide. Cyclophosphamide is metabolized in liver to acrolein. This is excreted in urine to cause damage to the bladder wall (Cox, 1979). About 5–10% of patients with a history of pelvic irradiation (Levenback et al, 1994) and up to 70% of patients exposed to high doses of cyclophosphamide or ifosfamide are at risk of developing hemorrhagic cystitis (Efros et al, 1990). Penicillins and danazol are reported to be associated with hemorrhagic cystitis (Bracis et al, 1977; Andriole et al, 1986; deVries and Freiha, 1990).

A. Signs and Symptoms

Gross hematuria with clots without evidence of typical urinary infection is a common symptom.

B. Differential Diagnosis

Malignancy, urinary tract infection, calculi, and benign prostate hyperplasia can cause gross hematuria.



▲ **Figure 38–7.** Cystoscopy of a patient with gross hematuria after radiation therapy of prostate cancer revealing diffuse bleeding at the bladder neck due to radiation-induced cystitis.

C. Diagnosis

Cystoscopy shows abnormal neovascularity that is easy to bleed with distention. Diffuse mucosal bleeding is common (Figure 38–7).

D. Prevention

For prevention of cyclophosphamide or ifosfamide-induced hemorrhage, hydration and continuous bladder drainage during chemotherapy are recommended (Ballen et al, 1999). 2-Mercaptoethane sulfonate binds to acrolein to reduce toxic effect, and it can be administered during the chemotherapy regimen (Goren et al, 1997).

E. Treatment

Bladder irrigation with a three-way catheter is essential. Oral ε-aminocaproic acid can be tried. Conservative therapy includes bladder irrigation with alum or silver nitrate. For severe hemorrhage with clot retention, cystoscopic clots evacuation, electrofulguration (Kaplan and Wolf, 2009), and formalin instillation in the bladder can be done under anesthesia (Donahue and Frank, 1989). A cystogram performed to confirm no association of vesicoureteral reflux prior to instillation is important since formalin can damage renal function if it were to reflux into the kidneys (Sarnak et al, 1999).

Giuliani et al (1979) have reported success by selective transcatheter embolization of the internal iliac arteries. Ostroff and Chenault (1982) believed that the best and least harmful method of treatment is continuous irrigation with 1% alum solution (the ammonium or potassium salt) through a three-way Foley catheter (Giuliani et al, 1979; Ostroff and Chenault, 1982). Alum can induce encephalopathy in renal failure patients, and careful monitoring of serum aluminum levels in such patients is recommended (Andriole et al, 1986; Perazella and Brown, 1993).

Hyperbaric oxygen therapy has been used for both radiation-induced and chemotherapy-induced hemorrhagic cystitis with encouraging results (Chong et al, 2005; Shao et al, 2012; Yoshida et al, 2008; Mougin et al, 2016). Conjugated estrogen therapy has also demonstrated some effect (Liu et al, 1990; Rodriguez et al, 1992; Miller et al, 1994).

Bilateral nephrostomy to reduce urinary contact to the bladder lumen is moderately effective. For severe refractory hematuria, cystectomy with urinary diversion or neobladder creation is considered as a last resort.

BENIGN PROSTATIC HYPERPLASIA

▶ Incidence and Epidemiology

Benign prostatic hyperplasia (BPH) is the most common benign tumor in men, and its incidence is age-related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41–50 years, to 50% in men aged 51–60 years, and upto 90% in men older than 80 years. Although clinical evidence of disease is available less commonly, symptoms of prostatic obstruction are also age-related. At age 55 years, approximately 25% of men report obstructive voiding symptoms. At age 75 years, 50% of men complain of a decrease in the force and caliber of their urinary stream.

Risk factors for the development of BPH are poorly understood. Some studies have suggested a genetic predisposition, and some have noted racial differences. Approximately 50% of men younger than 60 years who undergo surgery for BPH may have a heritable form of the disease. This form is most likely an autosomal dominant trait, and first-degree male relatives of such patients carry an increased relative risk of approximately fourfold.

▶ Etiology

The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine-controlled. The prostate is composed of both stromal and epithelial elements, and each, either alone or in combination, can give rise to hyperplastic nodules and the symptoms associated with BPH. Each element may be targeted in medical management schemes.

Observations and clinical studies in men have clearly demonstrated that BPH is under endocrine control. Castration results in the regression of established BPH and improvement in urinary symptoms. Additional investigations have demonstrated a positive correlation between levels of free testosterone and estrogen and the volume of BPH. The latter may suggest that the association between aging and BPH might result from the increased estrogen levels of aging causing induction of the androgen receptor, which thereby sensitizes the prostate to free testosterone. There is evidence that estrogens acting through stromal and epithelial estrogen receptors may contribute, in part, to diseases of the prostate. Genetic or environmental factors that influence 5 alpha-reductase appear to be important in the development of BPH as well (Kristal et al, 2008; Prins and Korach, 2008).

Pathology

As discussed earlier, BPH develops in the transition zone. It is truly a hyperplastic process resulting from an increase in cell number. Microscopic evaluation reveals a nodular growth pattern that is composed of varying amounts of stroma and epithelium. Stroma is composed of varying amounts of collagen and smooth muscle. The differential representation of the histologic components of BPH explains, in part, the potential responsiveness to medical therapy. Thus, beta-blocker therapy may result in excellent responses in patients with BPH that has a significant component of smooth muscle, while those with BPH composed predominantly of epithelium might respond better to 5 alpha-reductase inhibitors. Patients with significant components of collagen in the stroma may not respond to either form of medical therapy. Unfortunately, one cannot reliably predict responsiveness to a specific therapy (see later).

As BPH nodules in the transition zone enlarge, they compress the outer zones of the prostate, resulting in the formation of a so-called surgical capsule. This boundary separates the transition zone from the peripheral zone and serves as a surgical plane for enucleation of the prostate during open simple prostatectomies or holmium laser enucleation of the prostate procedures.

Pathophysiology

One can relate the symptoms of BPH to either the obstructive component of the prostate or the secondary response of the bladder to outlet resistance caused by the enlarged gland. The obstructive component can be subdivided into mechanical and dynamic forms of obstruction.

As prostatic enlargement occurs, mechanical obstruction may result from intrusion into the urethral lumen or bladder neck, leading to a higher bladder outlet resistance. Prior to the zonal classification of the prostate, urologists often referred to the “three lobes” of the prostate, namely, the two lateral lobes and the median lobe. Prostate size on digital rectal examination (DRE) correlates poorly with symptoms, in part because the median lobe is not readily palpable.

Dynamic obstruction explains the variable nature of the symptoms experienced by patients. The prostatic stroma, composed of smooth muscle and collagen, is rich in adrenergic nerve supply. The level of autonomic stimulation thus sets a tone to the prostatic urethra. Use of β-blocker therapy decreases this tone, resulting in a decrease in outlet resistance.

The irritative voiding complaints (see discussion later) of BPH result from the secondary response of the bladder to the increased outlet resistance. Bladder outlet obstruction leads to detrusor muscle hypertrophy and hyperplasia as well as collagen deposition. Although the latter is most likely responsible for a decrease in bladder compliance, detrusor instability is also a factor. On gross inspection, thickened detrusor muscle bundles are observed as trabeculation on cystoscopic examination. If left unchecked, mucosal herniation between detrusor muscle bundles ensues, causing diverticula formation (so-called false diverticula composed of mucosa and serosa without detrusor muscle present).

Clinical Findings

A. Symptoms

The symptoms of BPH can be divided into obstructive and irritative complaints. Obstructive symptoms include hesitancy, decreased force and caliber of stream, sensation of incomplete bladder emptying, double voiding (urinating a second time within 2 hours of the previous void), straining to urinate, and postvoid dribbling. Irritative symptoms include urgency, frequency, and nocturia.

The self-administered questionnaire originally developed by the American Urological Association (AUA) is both valid and reliable in identifying candidates for treatment and in monitoring treatment response. The AUA Symptom Score Questionnaire has been extensively validated and translated, and it is now more commonly known as the International Prostate Symptom Score (IPSS) (Table 38–2). The IPSS is perhaps the single most important tool used in the evaluation of patients with BPH and is recommended for all patients before the initiation of therapy. This assessment focuses on seven items that ask patients to quantify the severity of their obstructive or irritative complaints on a scale of 0 to 5. Thus, the score can range from 0 to 35. An IPSS of 0–7 is considered mild, 8–19 is considered moderate, and 20–35 is considered severe. The relative distribution of scores for BPH patients and control subjects is, respectively, 20% and 83% in those with mild scores, 57% and 15% in those with moderate scores, and 23% and 2% in those with severe scores (McConnell et al, 1994). As with other quality-of-life surveys, a reasonable degree of both literacy and numeracy is necessary for valid results. A multimedia version of the IPSS has been explored, which is more reliable among low-education populations (Bryant et al, 2009).

A detailed history focusing on the urinary tract excludes other possible causes of symptoms that may not result from the prostate, such as urinary tract infection, neurogenic bladder, urethral stricture, or prostate cancer.

B. Signs

A physical examination, DRE, and focused neurologic examination are performed during the clinical encounter. The size and consistency of the prostate are noted, even though prostate size, as determined by DRE, does not correlate with

Table 38–2. Questionnaire for international prostate symptom score.

Urinary symptoms (symptom score criteria)	AUA score						
	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinate?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 or more times	
7. Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
International Prostate Symptom Score (IPSS) = sum of questions A1 to A7							
Quality of life due to urinary problems							
	Delighted	Pleased	Mostly satisfied	Mixed—about equally satisfied and unsatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Reproduced with permission from McConnell JD: Benign Prostatic Hyperplasia; *Diagnosis and Treatment.* Clinical Practice Guideline No. 8. AHCPR Publication No. 94–0582. Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, Rockville, MD, 1994.

severity of symptoms or degree of obstruction. BPH usually results in a smooth, firm, elastic enlargement of the prostate. Induration, if detected, must alert the physician to the possibility of cancer and the need for further evaluation, namely, prostate-specific antigen (PSA), transrectal ultrasound (TRUS), consideration of prostate magnetic resonance imaging (MRI), and biopsy.

C. Laboratory Findings

A urinalysis to exclude infection or hematuria and serum creatinine measurement to assess renal function are required. Renal insufficiency may be observed in 10% of patients with prostatism and warrants upper-tract imaging. Patients with renal insufficiency are at increased risk of developing postoperative complications following surgical intervention for BPH. Serum PSA is considered optional, but most physicians will include it in the initial evaluation. PSA, compared with DRE alone, certainly increases the ability to detect prostate cancer, but because there is much overlap between levels seen in BPH and prostate cancer, its use remains controversial (see section on prostate cancer screening and chemoprevention).

D. Imaging

Upper tract imaging (renal ultrasound or computed tomography [CT] urogram) is recommended only in the presence of concomitant urinary tract disease or complications from BPH (eg, hematuria, urinary tract infection, renal insufficiency, history of stone disease). TRUS is useful to determine prostate size for men planning to undergo prostate surgery who are suspected to have severe prostate enlargement based on DRE.

E. Cystoscopy

Cystoscopy is not routinely recommended to determine the need for treatment but may assist in choosing the surgical approach in patients opting for invasive therapy. When marked obstructive symptoms exist in the setting of relative minimal prostate enlargement, cystoscopy may be useful to identify a high bladder neck, urethral stricture, or other pathology. If BPH is associated with hematuria, then cystoscopy is mandatory to rule out other bladder pathology.

F. Additional Tests

Measurement of flow rate, determination of postvoid residual urine, and pressure–flow studies are considered optional. Cystometrograms and urodynamic profiles are reserved for patients with suspected neurologic disease or those who have failed prostate surgery.

Differential Diagnosis

Other obstructive conditions of the lower urinary tract, such as urethral stricture, bladder neck contracture, bladder stone, or prostate cancer, must be entertained when evaluating men with presumptive BPH. A history of previous urethral instrumentation, urethritis, or trauma should be elucidated to exclude urethral stricture or bladder neck contracture. Hematuria and pain are commonly associated with bladder stones. Prostate cancer may be detected by abnormalities on the DRE or an elevated PSA (see discussion later).

A urinary tract infection, which can mimic the irritative symptoms of BPH, can be readily identified by urinalysis and culture; however, a urinary tract infection can also be a complication of BPH. Although irritative voiding complaints are also associated with carcinoma of the bladder, especially carcinoma in situ, the urinalysis usually shows evidence of hematuria. Likewise, patients with neurogenic bladder disorders may have many of the signs and symptoms of BPH, but a history of neurologic disease, stroke, diabetes mellitus, or back injury may be present as well. In addition, examination may show diminished perineal or lower extremity sensation or alterations in rectal sphincter tone or the bulbocavernosus reflex. Simultaneous alterations in bowel function (constipation) might also alert one to the possibility of a neurologic etiology.

Treatment

After patients have been evaluated, they should be informed of the various therapeutic options for BPH. It is advisable for patients to consult with their physicians to make an informed decision on the basis of the relative efficacy and side effects of the treatment options.

Specific treatment recommendations can be offered for certain groups of patients. For those with mild symptoms (IPSS score 0–7), watchful waiting is generally advised. On the other end of the therapeutic spectrum, absolute surgical indications include urinary retention refractory to medical management and attempts at catheter removal, recurrent urinary tract infection, recurrent gross hematuria, bladder stones, renal insufficiency, or large bladder diverticula.

A. Watchful Waiting

Very few studies on the natural history of BPH have been reported. The risk of progression or complications is uncertain. However, in men with symptomatic BPH, progression clearly is not inevitable, and some men will undergo spontaneous improvement or resolution of their symptoms.

Retrospective studies on the natural history of BPH are inherently subject to bias, related to patient selection and the type and extent of follow-up. Very few prospective studies addressing the natural history of BPH have been reported. A large randomized study compared finasteride with placebo in men with moderately to severely symptomatic BPH and enlarged prostates on DRE (McConnell et al, 1994). Patients in the placebo arm of the study had a 7% risk of developing urinary retention over 4 years.

As mentioned earlier, watchful waiting is the appropriate management of men with mild symptom scores (0–7). Men with moderate or severe symptoms can also be managed in this fashion if they so choose. Neither the optimal interval for follow-up nor specific end points for intervention have been defined.

B. Medical Therapy

1. **Alpha-Blockers**—The human prostate and bladder base contains alpha$_1$-adrenoreceptors, and the prostate shows a contractile response to corresponding agonists. The contractile properties of the prostate and bladder neck seem to be mediated primarily by the subtype alpha$_{1a}$-receptors. β-Blockade has been shown to result in both objective and subjective degrees of improvement in the symptoms and signs of BPH in some patients. beta-Blockers can be classified according to their receptor selectivity as well as their half-life (Table 38–3).

   Phenoxybenzamine and prazosin are the prototypical nonselective and selective beta-blockers, but today, they are primarily of historical interest.

   Long-acting beta$_1$-blockers make once-a-day dosing possible, but dose titration is still necessary. Terazosin is initiated at 1 mg daily for 3 days and increased to 2 mg daily for 11 days and then to 5 mg/day. Dosage can be escalated to 10 mg daily if necessary. Therapy with doxazosin is started at 1 mg daily for 7 days and increased to 2 mg daily for 7 days, and then to 4 mg daily. Dosage can be escalated to 8 mg daily if necessary. Possible side effects include orthostatic hypotension, dizziness, tiredness, retrograde ejaculation, rhinitis, and headache.

   Selective blockade of the alpha$_{1a}$-receptors, which are localized in the prostate and bladder neck, results in fewer systemic (particularly cardiovascular) side effects, thus obviating the need for dose titration with these agents (tamsulosin, alfuzosin, and silodosin). Other side effects such as retrograde ejaculation still can occur. Floppy iris syndrome, another potential side effect of alpha blockers, should be discussed with patients who may be considering cataract surgery.

Table 38–3. Classification of medical therapy and recommended dosage in BPH.

Classification	Oral dosage
α-Blockers	
Nonselective	
Phenoxybenzamine	10 mg twice a day
α1, short acting	
Prazosin	2 mg twice a day
α1, long acting	
Terazosin	5 or 10 mg daily
Doxazosin	4 or 8 mg daily
α$_{1a}$-Selective	
Tamsulosin	0.4 or 0.8 mg daily
Alfuzosin	10 mg daily
Silodosin	8 mg daily
5α-Reductase inhibitors	
Finasteride	5 mg daily
Dutasteride	0.5 mg daily

   Several randomized, double-blind, placebo-controlled trials, individually comparing beta-blockers with placebo, have demonstrated the safety and efficacy of all these agents.

2. **5α-Reductase inhibitors**—Finasteride is a 5 alpha-reductase inhibitor that blocks the conversion of testosterone to the more potent form, dihydrotestosterone (DHT). This drug affects the epithelial component of the prostate, resulting in a reduction in the size of the gland and improvement in symptoms. A 6-month duration of therapy is required to see the maximum effects on prostate size (30% reduction) and symptomatic improvement.

   Several randomized, double-blind, placebo-controlled trials have compared finasteride with placebo. Efficacy, safety, and durability are well established. However, symptomatic improvement is seen only in men with enlarged prostates (>40 cm^3). Side effects are uncommon and include decreased libido, decreased ejaculate volume, and impotence. Serum PSA is reduced by approximately 50% in patients being treated with finasteride, although individual values may vary.

   Dutasteride differs from finasteride as it inhibits both isoenzymes of 5 alpha-reductase. Similarly to finasteride, it reduces serum PSA and total prostate volume. Randomized, placebo-controlled trials have shown the efficacy of dutasteride in symptomatic relief, symptoms scores, peak urinary flow rate, and reduced risk of acute urinary retention and the need for surgery. Side effects are relatively uncommon and include erectile dysfunction, decreased libido, gynecomastia, and ejaculation disorders. Few studies have compared finasteride and dutasteride head-to-head. One retrospective analysis of >5000 men older than 65 years treated with 5α-reductase inhibitors in the mid-2000s found small but statistically significant differences, with rates of urinary retention of 12% and 14.7% for dutasteride and finasteride, respectively ($p < 0.0042$), and rates of prostate surgery of 3.9% and 5.1%, respectively ($p < 0.03$) (Fenter et al, 2008).

3. **Combination therapy**—The first randomized, double-blind, placebo-controlled study investigating combination alpha-blocker and 5 alpha-reductase inhibitor therapy was a four-arm Veterans Administration Cooperative Trial comparing placebo, finasteride alone, terazosin alone, and combination finasteride and terazosin (Lepor et al, 1996). More than 1200 patients participated, and significant decreases in IPSS and increases in urinary flow rates were seen only in the arms containing terazosin. However, one must note that an enlarged prostate was not

an entry criterion; in fact, prostate size in this study was much smaller than that in previous controlled trials using finasteride (32 vs 52 cm^3). McConnell and colleagues conducted a long-term, double-blind trial involving 3047 men to compare the effects of placebo, doxazosin, finasteride, and combination therapy on measures of the clinical progression of BPH (McConnell et al, 2003). The risk of overall clinical progression—defined as an increase above baseline of at least four points in the IPSS, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection—was significantly reduced by doxazosin (39% risk reduction) and finasteride (34% risk reduction), as compared with placebo. The reduction in risk associated with combination therapy (66% risk reduction) was significantly greater than that associated with doxazosin or finasteride alone. Patients most likely to benefit from combination therapy are those in whom baseline risk of progression is very high, generally patients with larger glands and higher PSA values.

4. **Phytotherapy—**The term **phytotherapy** refers to the use of plants or plant extracts for medicinal purposes. The use of phytotherapy in BPH has been popular in Europe for years, and its use in the United States has been explored as an alternative to pharmacologic agents. Currently, no phytotherapeutic agent is recommended by the AUA in the management of BPH.

C. Surgical Therapy

1. **Transurethral resection of the prostate (TURP)—**The vast majority of subtotal prostatectomies undertaken for BPH can be completed endoscopically. Most of these procedures involve the use of a spinal or general anesthetic and usually require an overnight hospital stay for observation for potential bleeding. Magnitude and durability of IPSS and flow rate improvement with transurethral resection of the prostate (TURP) are superior to those of any minimally invasive therapy. However, the length of hospitalization of patients undergoing TURP is greater. Risks of TURP include retrograde ejaculation (75%), impotence (5–10%), and incontinence (>1%). Complications include bleeding; urethral stricture or bladder neck contracture; perforation of the prostate capsule with extravasation; and, if severe, transurethral resection (TUR) syndrome resulting from a hypervolemic, hyponatremic state due to absorption of the hypotonic irrigating solution, although this is largely historical.

   Clinical manifestations of the TUR syndrome include nausea, vomiting, confusion, hypertension, bradycardia, and visual disturbances. The risk of the TUR syndrome increases with resection times of >90 minutes and is usually seen in older men. Treatment includes diuresis and, in severe cases, hypertonic saline administration. TURP can now be performed with a bipolar electrode, allowing resection to be performed under saline irrigation. This approach eliminates the hyponatremia responsible for TUR syndrome, although significant fluid volume absorption can still occur with prolonged resection.

2. **Transurethral incision of the prostate (TUIP)—**Men with moderate to severe symptoms and a small prostate often have posterior commissure hyperplasia (elevated bladder neck). These patients will often benefit from an incision of the prostate. This procedure is more rapid and less morbid than TURP. Outcomes in well-selected patients are comparable, although a lower rate of retrograde ejaculation with transurethral incision has been reported (25%). The technique involves two incisions using the Collins knife at the 5- and 7-o'clock positions. The incisions are started just distal to the ureteral orifices and are extended outward to the verumontanum.

3. **Transurethral vaporization of the prostate (TUVP)—**Ablative techniques use photo- or electroevaporation to ablate obstructing prostate tissue. The two most commonly used devices for these procedures are the neodymium-doped yttrium aluminum garnet (Nd:YAG) KTP "GreenLight" laser, which is preferentially absorbed by hemoglobin, and the plasma vaporization "Button" electrode. The latter works with a standard contemporary bipolar generator used for bipolar TURP.

   As with modern TURP, these procedures are performed under saline irrigation. The goal of the procedure in either case is to produce a central prostate defect comparable with what would be expected after a traditional TURP, but with less bleeding and lower risk of perforation. The potential downsides are greater irritative voiding symptoms in the short term after the procedure and less long-term durability of the result compared to a standard TURP. Also, as tissue is destroyed rather than resected, no specimen is sent to pathology for review.

4. **Holmium laser enucleation of the prostate (HoLEP)—**Rather than progressive resection or ablation of tissue from the urethra outward as with TURP and its derivatives, HoLEP denotes an anatomic dissection in the plane between the central and peripheral zones of the prostate. This approach is felt to provide the largest defect and perhaps the longest durability but entails a longer learning curve than TURP or TUVP. The enucleated prostate tissue may then be morcellated, extracted transurethrally, and sent to pathology for review.

5. **Simple (subtotal) prostatectomy—**When the prostate is too large to be removed endoscopically, an open enucleation is necessary. What constitutes "too large" is subjective and will vary depending on the surgeon's experience with TURP. Glands measuring >100 g are usually considered for open enucleation. Open prostatectomy may also be initiated when concomitant bladder diverticulum or a large bladder stone is present or if dorsal lithotomy positioning is not possible.

   Open prostatectomies can be done with either a suprapubic or retropubic approach. A **simple suprapubic**

prostatectomy is performed transvesically and is the operation of choice in dealing with concomitant bladder pathology. After the bladder is opened, a semicircular incision is made in the bladder mucosa, distal to the trigone. The dissection plane is initiated sharply, and then blunt dissection with the finger is performed to remove the adenoma. The apical dissection should be done sharply to avoid injury to the distal sphincteric mechanism. After the adenoma is removed, hemostasis is attained with suture ligatures, and both a urethral and a suprapubic catheter are inserted before closure. In a **simple retropubic prostatectomy**, the bladder is not entered. Rather, a transverse incision is made in the surgical capsule of the prostate, and the adenoma is enucleated as described earlier. Only a urethral catheter is needed at the end of the procedure. **Robot-assisted simple prostatectomy** has been reported, with research ongoing (Sutherland et al, 2011).

6. **Transurethral microwave thermotherapy (TUMT)**—Microwave hyperthermia is most commonly delivered with a transurethral catheter. Some devices cool the urethral mucosa to decrease the risk of injury. However, if temperatures are not >45°C, cooling is unnecessary. Improvement in IPSS and flow rate has been documented, but as these procedures are done in the office with no visual verification of tissue ablation, results have been mixed and difficult to predict who will respond well. Strong financial incentives, however, have driven frequent utilization in certain clinical contexts.

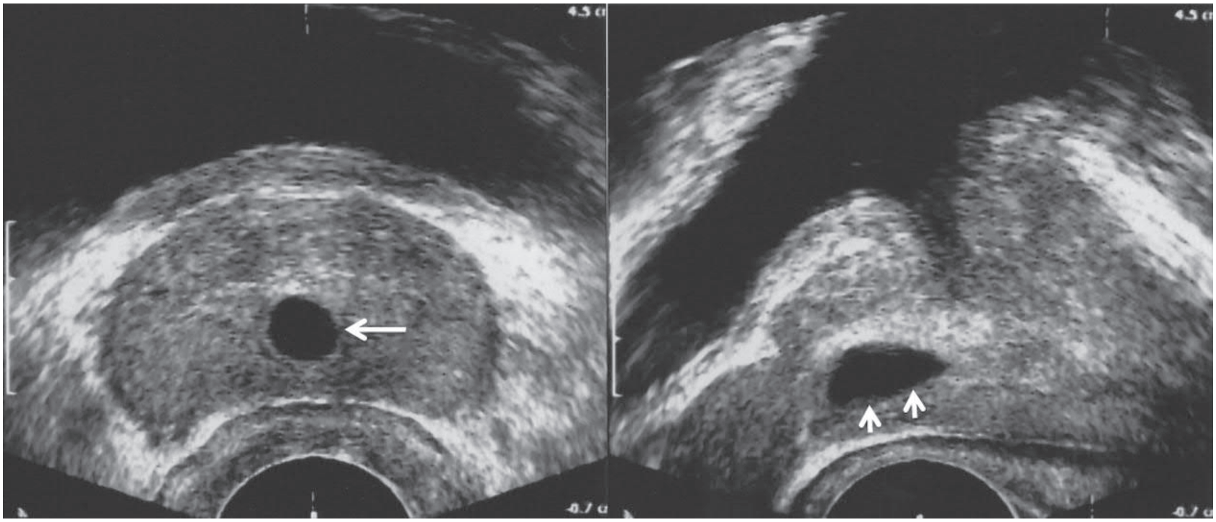
   Very sparse prospective data are available to fairly compare any of the above procedures with TURP or with each other. A meta-analysis found few differences, but the component studies tended to be small and with limited follow-up (Ahyai et al, 2010). All the newer procedures are more expensive than TURP, and comparative cost-effectiveness studies are sorely needed.

7. **Prostatic urethral lift (Urolift)**—When the patient is noted to have symptomatic LUTS with obstructing lateral lobes, prostatic urethral lift procedure may be considered. This day procedure uses permanent implants placed into the lateral lobes to compress the obstructing tissue and open the urethral lumen. Contraindications include presence of a median lobe, a high bladder neck, or larger prostate glands (>100 g).
8. **Water vapor therapy (Rezum)**—This day procedure can be performed under sedation and can be used in men with a median lobe. During transurethral procedure water vapor is injected into the transition zone of the prostate. Using convective heat transfer, this causes acute necrosis as the water vapor condenses to water within the injected prostatic tissue. The area is irrigated with saline, which aids in cooling the tissue.

ANOMALIES OF THE PROSTATE AND SEMINAL VESICLES

Prostatic Cysts and Calculi

Cysts in the prostate gland are very common. Enlargements of the prostatic utricle are often found at the time of transrectal ultrasonography. Those cysts are usually small, lying in the midline posterior to the prostatic urethra and typically appear in teardrop shape in sagittal view (Figure 38–8).



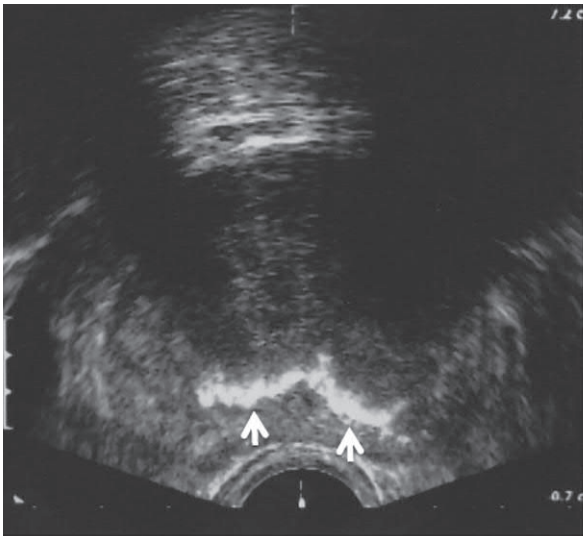
▲ **Figure 38–8.** Transrectal ultrasonography demonstrating typical utricular cyst. Transverse image at the base shows a round cyst (*arrow*) in the midline posterior to the urethra (***left***). On sagittal view, the cyst is typical teardrop shape (*arrowheads*) with the narrow end extends toward the urethra (***right***).

These cysts represent embryologic remnants of the distal end of the Müllerian ducts. Those midline cysts commonly have communication with the urethra; however, some variants are known to exist (Furuya et al, 2008; Kato et al, 2005). Most of these cysts are asymptomatic and are found incidentally. Occasionally, cysts may hemorrhage and cause hematospermia (Coppens et al, 2002). Rarely, they become large enough to be easily palpable rectally or even abdominally. Through local pressure, they may cause symptoms of obstruction of the bladder neck (Desautel et al, 1999). Utricular cysts may cause obstruction of the ejaculatory ducts (Sharlip, 1984). This condition can be discovered during the male infertility workup. Ejaculatory ducts may open in the midline cyst (Furuya et al, 2008). Other common cysts in the prostate are degenerative cysts. Those cysts are commonly seen in the transition zone of the enlarged gland; however, multiple cysts can also be seen in the peripheral zone. Those cysts cause no symptoms.

Prostatic calculi are a very common condition. Almost all middle-aged men will have generally prostatic calculi. Prostatic calculi commonly develop in the prostatic duct near prostatic urethra. Prostatic calculi are commonly found during transrectal ultrasonography of the prostate (Figure 38–9). In general, prostatic calculi cause no symptoms. However, patients with massive prostatic calculi may have voiding dysfunction to cause urine reflux into the prostatic ducts (Kim et al, 2011).

Anomalies of the Seminal Vesicle

Unilateral or bilateral agenesis of the seminal vesicle is often discovered during an infertility workup. Agenesis of the seminal vesicle is generally asymptomatic except for low ejaculatory volume. On examination, vas deferens on the affected side may be absent. Agenesis or ectopic location of the affected side kidney can also be found.



▲ **Figure 38–9.** Typical prostatic calculi on transrectal ultrasonography are shown as curved bright lines (*arrows*) with acoustic shadows.

Ectopic ureteral opening in the ejaculatory duct causes extremely dilated ampulla of vas deferens and seminal vesicle. These patients often have a history of recurrent epididymitis on the affected side. The kidney on the affected side is frequently ectopic and dysplastic or manifest agenesis (Carbone et al, 2007; Cherullo et al, 2002).

BIBLIOGRAPHY

Ahyai SA et al: Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. Eur Urol 2010;58:384–397.

al-Hindawi MK, Aman S: Benign non-infected urachal cyst in an adult: Review of the literature and a case report. Br J Radiol 1992;65:313–316.

Amendola MA et al: Detection of occult colovesical fistula by the Bourne test. Am J Roentgenol 1984;142:715–718.

Andriole GL et al: Danazol-induced cystitis: an undescribed source of hematuria in patients with hereditary angioneurotic edema. J Urol 1986;135:44–46.

Austin PF et al: The prenatal diagnosis of cloacal exstrophy. J Urol 1998;160:1179–1181.

Ayhan A et al: Results of treatment in 182 consecutive patients with genital fistulas. Int J Gynaecol Obstet 1995;48:43–47.

Badlani G et al: Enterovesical fistulas in crohn disease. Urology 1980;16:599–600.

Ballen KK et al: Safety and cost of hyperhydration for the prevention of hemorrhagic cystitis in bone marrow transplant recipients. Oncology 1999;57:287–292.

Baskin LS, Tanagho EA: Pelvic pain without pelvic organs. J Urol 1992;147:683–686.

Bauer SB, Retik AB: Urachal anomalies and related umbilical disorders. Urol Clin North Am 1978;5:195–211.

Berry SH et al: Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. J Urol 2011;186:540–544.

Bhat A et al: Congenital bladder diverticulum presenting as bladder outlet obstruction in infants and children. J Pediatr Urol 2012; 8:348–353.

Bjørnerem A, Tollan A: Intrauterine device—primary and secondary perforation of the urinary bladder. Acta Obstet Gynecol Scand 1997;76:383–385.

Bjurlin MA, Berger AD: Herniorrhaphy mesh as nidus for bladder calculi. Urology 2011;78(2):329–330.

Bjurlin MA et al: Imaging the high-risk prostate cancer patient: Current and future approaches to staging. Urology 2018;116:3–12.

Blaivas JG et al: Early versus late repair of vesicovaginal fistulas: Vaginal and abdominal approaches. J Urol 1995;153:1110–1112, discussion 1112–1113.

Blane CE et al: Bladder diverticula in children. Radiology 1994;190:695–697.

Bogdanos J et al: The large bladder diverticulum in children. J Pediatr Urol 2005;1:267–272.

Bracis R et al: Methicillin hemorrhagic cystitis. Antimicrob Agents Chemother 1977;12:438–439.

Brusky JP et al: Removal of an unusual foreign body from the bladder and urethra. J Trauma 2008;65:1568.

Bryant MD et al: Multimedia version of a standard medical questionnaire improves patient understanding across all literacy levels. J Urol 2009;182:1120–1125.

Buffington CAT: Comorbidity of interstitial cystitis with other unexplained clinical conditions. J Urol 2004;172:1242–1248.

Burbige KA et al: The megacystis-megaureter syndrome. J Urol 1984;131:1133–1136.

Burkman RT: Chronic pelvic pain of bladder origin: Epidemiology, pathogenesis and quality of life. J Reprod Med 2004;49: 225–229.

Carbone A et al: Renal aplastic dysplasia and ipsilateral ectopic ureter obstructing the seminal via: A possible cause of male infertility. Eur Urol 2007;52:268–272.

Cardozo L: Recurrent intra-vesical foreign bodies. Br J Urol 1997; 80:687.

Catalano O: US evaluation of inguinoscrotal bladder hernias: Report of three cases. Clin Imaging 1997;21:126–128.

Cervellione RM et al: Prospective study on the incidence of bladder/cloacal exstrophy and epispadias in Europe. J Pediatr Urol 2015; 11:337.e1–337.e6.

Cervellione RM: The use of pelvic osteotomy in cloacal exstrophy. Semin Pediatr Surg 2011;20:119–122.

Chaiken DC et al: Behavioral therapy for the treatment of refractory interstitial cystitis. J Urol 1993;149:1445–1448.

Chan ESY et al: Novel approach of laparoscopic transperitoneal en bloc resection of urachal tumor and umbilectomy with a comparison of various techniques. J Laparoendosc Adv Surg Tech 2009;19:423–426.

Chandhoke RA, Ghoniem GM: Transurethral electrovaporization of bladder diverticulum: An alternative to open or laparoscopic bladder diverticulectomy. J Endourol Case Rep 2015;1:11–13.

Chapple CR et al: Subtrigonal phenol injection. How safe and effective is it? Br J Urol 1991;68:483–486.

Cherullo EE et al: Laparoscopic management of congenital seminal vesicle cysts associated with ipsilateral renal agenesis. J Urol 2002;167:1263–1267.

Chong KT et al: Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. Urology 2005;65:649–653.

Chouhan M et al: Utility of diffusion-weighted imaging in the presurgical diagnosis of an infected urachal cyst. Pediatr Radiol 2010;41:125–128.

Chuang Y-T et al: Laparoscopic removal of a migrated intrauterine contraceptive device with bladder penetration. Taiwan J Obstet Gynecol. 2010;49:518–520.

Cilento BG Jr et al: Urachal anomalies: Defining the best diagnostic modality. Urology 1998;52:120–122.

Clemens JQ et al: Case-control study of medical comorbidities in women with interstitial cystitis. J Urol 2008;179:2222–2225.

Comiter CV: Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: A prospective study. J Urol 2003;169:1369–1373.

Confer SD et al: Megacystis with an anterior urethral valve: Case report and review of literature. J Pediatr Urol 2010;6:459–462.

Coppens L et al: Adult müllerian duct or utricle cyst: Clinical significance and therapeutic management of 65 cases. J Urol 2002;167:1740–1744.

Cox PJ: Cyclophosphamide cystitis—identification of acrolein as the causative agent. Biochem Pharmacol 1979;28:2045–2049.

Desautel MG et al: Müllerian duct remnants: Surgical management and fertility issues. J Urol 1999;162:1008–1013, discussion 1014.

Destri GL et al: The Urachal pathology with umbilical manifestation: Overview of laparoscopic technique. J Laparoendosc Adv Surg Tech 2011;21:809–814.

deVries CR, Freiha FS: Hemorrhagic cystitis: A review. J Urol 1990;143:1–9.

Donahue LA, Frank IN: Intravesical formalin for hemorrhagic cystitis: Analysis of therapy. J Urol 1989;141:809–812.

Efros M et al: Cyclophosphamide-induced hemorrhagic pyelitis and ureteritis associated with cystitis in marrow transplantation. J Urol 1990;144:1231–1232.

Elbadawi A: Interstitial cystitis: A critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. Urology 1997;49:14–40.

Emanuel PG et al: Prenatal detection of anterior abdominal wall defects with US. RadioGraphics 1995.

Feldkamp ML et al Cloacal exstrophy: An epidemiologic study from the International Clearinghouse for Birth Defects Surveillance and Research. American Journal of Medical Genetics Part C: Seminars in Medical Genetics. John Wiley & Sons, Ltd; 2011 Nov 15;157(4):333–43.

Fenter TC et al: Dutasteride vs finasteride: assessment of differences in acute urinary retention rates and surgical risk outcomes in an elderly population aged > or =65 years. Am J Manage Care 2008;14:S154–S159.

Fontanella F et al: Fetal megacystis: Prediction of spontaneous resolution and outcome. Ultrasound Obstet Gynecol 2017;50:458–463.

Foster HE et al: Effect of amitriptyline on symptoms in treatment [of] naïve patients with interstitial cystitis/painful bladder syndrome. J Urol 2010;183:1853–1858.

Fu L-Y, Adeniran AJ: Adenocarcinoma arising from a bladder diverticulum. J Urol 2015;194:527–528.

Furuya R et al: New classification of midline cysts of the prostate in adults via a transrectal ultrasonography-guided opacification and dye-injection study. BJU Int 2008;102:475–478.

Gambhir L et al: Epidemiological Survey of 214 Families With Bladder Exstrophy-Epispadias Complex. Journal of Urology. 2008 Apr 1; 179(4):1539–43.

Gargollo P et al: Bladder neck reconstruction is often necessary after complete primary repair of exstrophy. J Urol 2011;185: 2563–2571.

Gargollo PC, Borer JG: Contemporary outcomes in bladder exstrophy. Curr Opin Urol 2007;17:272–280.

Gerridzen RG, Futter NG: Ten-year review of vesical diverticula. Urology 1982;20:33–35.

Gillenwater JY, Wein AJ: Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28–29, 1987. J Urol 1988;140:203–206.

Gilmour DT et al: Lower urinary tract injury during gynecologic surgery and its detection by intraoperative cystoscopy. Obstet Gynecol 1999;94:883–889.

Giuliani L et al: Gelatin foam and isobutyl-2-cyanoacrylate in the treatment of life-threatening bladder haemorrhage by selective transcatheter embolisation of the internal iliac arteries. Br J Urol 1979;51:125–128.

Gopalan A et al Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. The American Journal of Surgical Pathology. NIH Public Access; 2009 May;33(5): 659–68.

Goren MP et al: Combined intravenous and oral mesna in outpatients treated with ifosfamide. Cancer Chemother Pharmacol 1997;40:371–375.

Grady RW et al: Complete primary closure of bladder exstrophy: Epispadias and bladder exstrophy repair. Urol Clin North Am 1999;26:95–109.

Grubišić I et al: Intravesical foreign body as a result of self catheterization: case report. Acta Clin Croat 2014;53:359–361.

Gupta AD et al: Examining long-term outcomes of bladder exstrophy: A 20-year follow-up. BJU Int 2014;113:137–141.

Heyns CF et al: Pelvic lipomatosis associated with cystitis glandularis and adenocarcinoma of the bladder. J Urol 1991;145:364–366.

Hick EJ et al: Bladder calculus resulting from the migration of an intrauterine contraceptive device. J Urol 2004;172:1903.

Holten I et al: The ultrasonic diagnosis of Urachal anomalies. Australas Radiol 1996;40:2–5.

Huang WC et al: Surgical repair of vesicovaginal fistulas. Urol Clin North Am 2002;29:709–723.

Huettner PC et al: Colouterine fistula complicating diverticulitis: charcoal challenge test aids in diagnosis. Obstet Gynecol 1992;80:550–552.

Hurst RE et al: Urinary glycosaminoglycan excretion as a laboratory marker in the diagnosis of interstitial cystitis. J Urol 1993;149:31–35.

Husmann DA, Rathbun SR: Long-term follow up of enteric bladder augmentations: The risk for malignancy. J Pediatr Urol 2008;4:381–385.

ICBDMS (International Clearinghouse for Birth Defects Monitoring Systems): Epidemiology of bladder exstrophy and epispadias: A communication from the international clearinghouse for birth defects monitoring systems. Teratology 1987;36:221–227.

Jayachandran D et al: Register based study of bladder exstrophy-epispadias complex: Prevalence, associated anomalies, prenatal diagnosis and survival. J Urol 2011;186:2056–2061.

Jin C et al: Removal of foreign bodies embedded in the urinary bladder wall by a combination of laparoscopy and carbon dioxide cystoscopic assistance: Case report and literature review. Investig Clin Urol 2016;57:449–452.

Johansson SL, Fall M: Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol 1990;143: 1118–1124.

Joseph RC et al: Genitourinary tract gas: Imaging evaluation. RadioGraphics 1996;16:295–308.

Kaplan JR, Wolf JS: Efficacy and survival associated with cystoscopy and clot evacuation for radiation or cyclophosphamide induced hemorrhagic cystitis. J Urol 2009;181:641–646.

Kato H et al: Anatomical and histological studies of so-called Müllerian duct cyst. Int J Urol 2005;12:465–468.

Khonsari S et al: Intraoperative catheter management during laparoscopic excision of a giant bladder diverticulum. J Laparoendosc Adv Surg Tech 2004;14:47–50.

Kiddoo DA et al: Initial management of complex urological disorders: Bladder exstrophy. Urol Clin North Am 2004;31:417–426, vii–viii.

Kim WB et al: Influence of prostatic calculi on lower urinary tract symptoms in middle-aged men. Urology 2011;78:447–449.

Kirsh GM et al: Diagnosis and management of vesicoenteric fistulas. Surg Gynecol Obstet 1991;173:91–97.

Kristal AR et al: Serum steroid and sex hormone-binding globulin concentrations and the risk of incident benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol 2008;168:1416–1424.

Kural AR et al: Robot-assisted laparoscopic bladder diverticulectomy combined with photoselective vaporization of prostate: A case report and review of literature. J Endourol 2009;23:1281–1285.

Kusek JW, Nyberg LM: The epidemiology of interstitial cystitis: Is it time to expand our definition? Urology 2001;57:95–99.

Kwon EO et al: The poppy seed test for colovesical fistula: Big bang, little bucks! J Urol 2008;179:1425–1427.

Lepor H et al: The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. New Engl J Med 1996;335:533–539.

Levenback C et al: Hemorrhagic cystitis following radiotherapy for stage Ib cancer of the cervix. Gynecol Oncol 1994;55:206–210.

Light JK, Scott FB: Treatment of the epispadias-exstrophy complex with the AS792 artificial urinary sphincter. J Urol 1983; 129:738–740.

Liu YK et al: Treatment of radiation or cyclophosphamide induced hemorrhagic cystitis using conjugated estrogen. J Urol 1990;144:41–43.

Lowentritt BH et al: Variants of the exstrophy complex: A single institution experience. J Urol 2005;173:1732–1737.

Macejko AM et al: Cystoscope- and robot-assisted bladder diverticulectomy. J Endourol 2008;22:2389–2391, discussion 2391–2392.

Mastromichalis M et al: Urethral foreign body insertion for secondary gain in the incarcerated population. Can J Urol 2011;18:5916–5917.

Masumori N, Tsukamoto T: Pelvic lipomatosis associated with proliferative cystitis: Case report and review of the Japanese literature. Int J Urol 1999;6:44–49.

McConnell JD et al: Benign prostatic hyperplasia: diagnosis and treatment. Agency for Health Care Policy and Research. Clin Pract Guide Quick Ref Guide Clin 1994. pp. 1–17.

McConnell JD et al: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. New Engl J Med 2003;349:2387–98.

McCormack K et al: Laparoscopic surgery for inguinal hernia repair: Systematic review of effectiveness and economic evaluation. Health Technol Assess 2005;9:1–203, iii–iv.

McKay HA: Vesicovaginal fistula repair: Transurethral suture cystorrhaphy as a minimally invasive alternative. J Endourol 2004;18:487–490.

Melchior S et al: Diagnosis and surgical management of colovesical fistulas due to sigmoid diverticulitis. J Urol 2009;182:978–982.

Meldrum KK et al: Pelvic and extremity immobilization after bladder exstrophy closure: Complications and impact on success. Urology 2003;62:1109–1113.

Mesrobian H-GO et al: Ten years of experience with isolated Urachal anomalies in children. J Urol 1997;158:1316–1318.

Miglani U et al: Rare etiology of obstructive uropathy: Pelvic lipomatosis. Urol Int 2010;84:239–241.

Miller J et al: Oral conjugated estrogen therapy for treatment of hemorrhagic cystitis. J Urol 1994;151:1348–1350.

Mitchell ME: Bladder exstrophy repair: Complete primary repair of exstrophy. Urology 2005;65:5–8.

Mollard P et al: Urinary continence after reconstruction of classical bladder exstrophy (73 cases). Br J Urol 1994;73:298–302.

Moon SG et al: Pelvic fistulas complicating pelvic surgery or diseases: Spectrum of imaging findings. Korean J Radiol 2001;2:97–104.

Mordkin RM et al: The radiographic diagnosis of pelvic lipomatosis. Tech Urol 1997;3:228–230.

Moss RL, Ryan JA: Management of enterovesical fistulas. Am J Surg 1990;159:514–517.

Mougin J et al: Evaluation of hyperbaric oxygen therapy in the treatment of radiation-induced hemorrhagic cystitis. Urology 2016;94:42–46.

Mourtzinos A, Borer JG: Current management of bladder exstrophy. Curr Urol Rep Curr Med Group 2004;5:137–141.

Nickel JC, Emerson L, Cornish J. The Bladder Mucus (Glycosaminoglycan) Layer in Interstitial Cystitis. Journal of Urology. No longer published by Elsevier; 1993 Apr 1;149(4):716–8.

Nickel JC: Interstitial cystitis: A chronic pelvic pain syndrome. Med Clin North Am 2004;88:467–481, xii.

Nordling J: Interstitial cystitis: How should we diagnose it and treat it in 2004? Curr Opin Urol 2004;14:323–327.

Oberpenning F et al: Interstitial cystitis: An update. Curr Opin Urol 2002;12:321–332.

Oesterling JE, Jeffs RD: The importance of a successful initial bladder closure in the surgical management of classical bladder exstrophy: Analysis of 144 patients treated at the Johns Hopkins Hospital between 1975 and 1985. J Urol 1987;137:258–262.

O'Leary MP et al: The interstitial cystitis symptom index and problem index. Urology 1997;49:58–63.

Ostroff EB, Chenault OW: Alum irrigation for the control of massive bladder hemorrhage. J Urol 1982;128:929–930.

Ottem DP, Teichman JMH: What is the value of cystoscopy with hydrodistension for interstitial cystitis? Urology 2005;66:494–499.

Parsons CL, Mulholland SG: Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol 1987;138:513–516.

Patle NM et al: Sliding inguinal hernias: Scope of laparoscopic repair. J Laparoendosc Adv Surg Tech A 2011;21:227–231.

Perazella M, Brown E: Acute aluminum toxicity and alum bladder irrigation in patients with renal failure. Am J Kidney Dis 1993;21:44–46.

Perlmutter AD et al: Vesical neck reconstruction in patients with epispadias-exstrophy complex. J Urol 1991;146:613–615.

Persky L et al: Nondelay in vesicovaginal fistula repair. Urology 1979;13:273–275.

Peters KM et al: Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. Urology 2007;70:16–18.

Pham KN et al: Endoscopic management of bladder diverticula. Rev Urol 2016;18:114–117.

Pieretti RV, Pieretti-Vanmarcke RV. Congenital bladder diverticula in children. J Pediatr Surg 1999;34:468–473.

Popescu O-E et al: The spectrum of eosinophilic cystitis in males: Case series and literature review. Arch Pathol Lab Med 2009;133:289–294.

Prakash et al: Urinary bladder diverticulum and its association with malignancy: An anatomical study on cadavers. Rom J Morphol Embryol 2010;51:543–545.

Prins GS, Korach KS: The role of estrogens and estrogen receptors in normal prostate growth and disease. Steroids 2008;73:233–244.

Raghavaiah NV: Double-dye test to diagnose various types of vaginal fistulas. J Urol 1974;112:811–812.

Rodriguez Luna JM et al: Control of massive hematuria in idiopathic hemorrhagic cystitis after administration of conjugated estrogen. J Urol 1992;148:1524–1525.

Rubin L, Pincus MB: Eosinophilic cystitis: The relationship of allergy in the urinary tract to eosinophilic cystitis and the pathophysiology of eosinophilia. J Urol 1974;112:457–460.

Sairanen J et al: Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: A randomized comparative study. J Urol 2005;174:2235–2238.

Salman M et al: Eosinophilic cystitis simulating invasive bladder cancer: A real diagnostic challenge. Int Urol Nephrol 2006;38: 545–548.

Sant GR et al: A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003;170:810–815.

Sarnak MJ et al: Intravesicular formaldehyde instillation and renal complications. Clin Nephrol 1999;51:122–125.

Scheye T et al: Anatomic basis of pathology of the urachus. Surg Radiol Anat 1994;16:135–41.

Sebire NJ et al: Fetal megacystis at 10–14 weeks of gestation. Ultrasound Obstet Gynecol 1996;8:387–390.

Shao Y et al: Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int 2012;109:691–694.

Sharlip ID: Obstructive azoospermia or oligozoospermia due to Müllerian duct cyst. Fertil Steril 1984;41:298–303.

Simon LJ et al: The Interstitial Cystitis Data Base Study: Concepts and preliminary baseline descriptive statistics. Urology 1997;49:64–75.

Simoneaux SF, Patrick LE: Genitourinary complications of Crohn's disease in pediatric patients. Am J Roentgenol 1997;169:197–199.

Sirinian E et al: Correlation between 2 interstitial cystitis symptom instruments. J Urol 2005;173:835–840.

Sözen S et al: The importance of re-evaluation in patients with cystitis glandularis associated with pelvic lipomatosis: A case report. Urol Oncol 2004;22:428–430.

Stamatiou K, Moschouris H: A rubber tube in the bladder as a complication of autoerotic stimulation of the urethra. Arch Ital Urol Androl 2016;88:239–240.

Stec AA et al: The modern staged repair of classic bladder exstrophy: A detailed postoperative management strategy for primary bladder closure. J Pediatr Urol 2012;8:549–555.

Stone NM et al: Laparoscopic excision of a urachal cyst. Urology 1995;45:161–164.

Suskind AM et al: The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND Interstitial Cystitis Epidemiology male study. J Urol 2013;189:141–145.

Suson KD et al: Bony abnormalities in classic bladder exstrophy: The urologist's perspective. J Pediatr Urol 2013;9:112–122.

Sutherland DE et al: Robot-assisted simple prostatectomy for severe benign prostatic hyperplasia. J Endourol 2011;25:641–644.

Tamam M et al: Direct radionuclide cystography imaging in colovesical fistula due to inguinal hernia operation complication. Ann Nucl Med 2009;23:693–696.

Taskinen S, Suominen JS: Lower urinary tract symptoms (LUTS) in patients in adulthood with bladder exstrophy and epispadias. BJU Int 2013;111:1124–1129.

Theoharides TC: Hydroxyzine in the treatment of interstitial cystitis. Urol Clin North Am 1994;21:113–119.

Thilagarajah R et al: Oral cimetidine gives effective symptom relief in painful bladder disease: A prospective, randomized, double-blind placebo-controlled trial. BJU Int 2001;87:207–212.

Thompson RH et al: Clinical manifestations and functional outcomes in children with eosinophilic cystitis. J Urol 2005;174:2347–2349.

Upadhyay V, Kukkady A: Urachal remnants: An enigma. Eur J Pediatr Surg 2004;13:372–376.

van Ophoven A et al: A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. J Urol 2004;172:533–536.

Vining NC et al: Classic bladder exstrophy: Orthopaedic surgical considerations. J Am Acad Orthop Surg 2011;19:518.

Walker NF et al: Diagnosis and management of intradiverticular bladder tumours. Nat Rev Urol 2014;11:383–390.

Watanabe M et al: [A case of eosinophilic cystitis that was treated with oral suplatast tosilate (IPD-1151T).] Hinyokika Kiyo 2009;55: 715–719.

Wesselmann U: Neurogenic inflammation and chronic pelvic pain. World J Urol 2001;19:180–185.

Yohannes P et al: Laparoscopic radical excision of Urachal sinus. J Endourol 2004;17:475–479.

Yoshida T et al: Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. Int J Urol 2008;15:639–641.

Yu C-C et al: Intradiverticular tumors of the bladder: Surgical implications–an eleven-year review. Eur Urol 1993;24:190–196.

Male Sexual Dysfunction

39

Amanda B. Reed-Maldonado, MD, FACS; &
Tom F. Lue, MD

BACKGROUND AND INTRODUCTION

It is estimated that more than half of men aged 40–70 in the United States are unable to attain or maintain a penile erection sufficient for satisfactory sexual performance. Advances in pharmacologic therapy for erectile dysfunction (ED), coupled with a better understanding of male sexual dysfunction, have resulted in greater numbers of patients seeking care for sexual concerns. Oral phosphodiesterase type 5 inhibitors have emerged as the preferred first-line treatment of ED worldwide because of their efficacy, ease of use, and patient safety. Erectile function can now be evaluated by the response to these agents at home or by assessment of response to intracavernous injection (ICI) of vasoactive agents in the office, and improved diagnostic tests can differentiate among types of impotence. Patient satisfaction with penile prostheses is high, as the latest generation of devices is more sophisticated and durable than ever. Current treatments continue to evolve and new therapies, such as low-intensity extracorporeal shockwave, stem cell, and gene therapies, may represent the next generation of more physiologic and disease-specific solutions to various types of ED (Melman et al, 2007; Lin et al, 2017; Bahk et al, 2010).

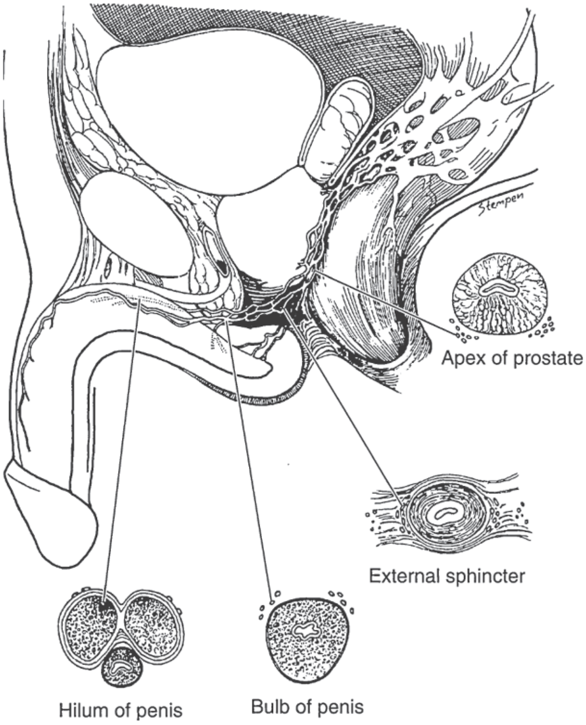
PHYSIOLOGY OF PENILE ERECTION

Innervation of the Penis

The autonomic spinal erection center is located in the intermediolateral nuclei of the spinal cord at levels S2–S4 and T12–L2. Nerve fibers from the thoracolumbar (sympathetic) and sacral (parasympathetic) spinal segments join to form the inferior hypogastric and pelvic plexuses, which send branches to the pelvic organs. The fibers innervating the penis (cavernous nerves) travel along the posterolateral aspect of the seminal vesicles and prostate and then accompany the membranous urethra through the genitourinary diaphragm (Figure 39–1). Some of these fibers enter the corpora cavernosa and corpus spongiosum with the cavernous and bulbourethral arteries. Others travel distally with the dorsal nerve and enter the corpus cavernosum and corpus spongiosum in various locations to supply the middle and distal portions of the penis. The terminal branches of the cavernous nerves innervate the helicine arteries and trabecular muscle, and are responsible for vascular events during tumescence and detumescence.

The center for somatic motor nerves is located at the ventral horn of the S2–S4 segments (Onufs nucleus). The motor fibers join the pudendal nerve to innervate the bulbocavernosus and ischiocavernosus muscles. The somatic sensory nerves originate at receptors in the penis to transmit pain, temperature, touch, and vibratory sensations. The brain has a modulatory effect on the spinal pathways of erection, specifically the medial preoptic area and paraventricular nucleus of the hypothalamus, the periaqueductal gray area of the midbrain, and the nucleus paragigantocellularis of the medulla. Positron emission tomography (PET) and functional magnetic resonance imaging (MRI) have allowed for greater understanding of brain activation during sexual arousal and orgasm by measuring regional cerebral blood flow or activity. These powerful tools, used in the study of higher brain function and central activation of sexual arousal, may better define pathophysiology associated with varied conditions including psychogenic ED, premature ejaculation, and orgasmic dysfunction (Georgiadis and Holstege, 2005).

Three types of erections are noted in humans: (1) genital-stimulated (contact or reflexogenic), (2) central-stimulated (noncontact or psychogenic), and (3) central-originated (nocturnal). Genital-stimulated erection is induced by tactile stimulation of the genital area. This kind of erection can be preserved in upper spinal cord lesions, although erections are usually short in duration and poorly controlled by the individual. Central-stimulated erection is more complex, resulting from memory,



▲ **Figure 39–1.** Location of cavernous nerves in relation to urethra.

fantasy, visual, or auditory stimuli. Centrally originated erections can occur spontaneously without stimulation or during sleep; most sleep erections occur during rapid eye movement (REM) sleep.

▶ Anatomy and Hemodynamics of Penile Erection

The tunica of the corpora cavernosa is a bilayered structure with multiple sublayers. The inner circular bundles support and contain the cavernous tissue. From this inner layer, intracavernosal pillars that act as struts radiate to augment the septum; both structures provide structural support to the corpus cavernosum. The outer-layer bundles are oriented longitudinally and extend from the glans penis to the proximal crura. These fibers insert into the inferior pubic ramus but are absent between the 5- and 7-o'clock positions. In contrast, the corpus spongiosum lacks an outer layer or intracorporeal struts, ensuring a lower pressure structure during erection. The tunica is composed of elastic fibers forming a network on which the collagen fibers rest. Emissary veins run between the inner and outer layers for a short distance, often piercing the outer bundles obliquely. Branches of the dorsal artery take a more direct perpendicular route and are surrounded by a periarterial fibrous sheath (Hsu et al, 2004).

The paired internal pudendal arteries are the major carriers of the blood supply to the penis, dividing into three branches: the bulbourethral artery, the dorsal artery, and the cavernous artery (deep artery). The cavernous artery supplies the corpora cavernosa; the dorsal artery, the skin, subcutaneous tissue, and the glans penis; and the bulbourethral artery, the corpus spongiosum. In some men, accessory pudendal arteries from external iliac or obturator arteries may supply a major portion of the penis, with collaterals among the three branches often observed. The venous drainage of the glans is mainly through the deep dorsal vein. The corpus spongiosum is drained via the circumflex, urethral, and bulbar veins, but the drainage of the corpora cavernosa is more complex: the mid- and distal shaft are drained by the deep dorsal and periarterial veins to the preprostatic plexus, while the proximal portion is drained by the cavernous and crural veins to the preprostatic plexus and internal pudendal vein. The drainage of all three corpora originates in the subtunical venules, which unite to form emissary veins. The glans penis possesses numerous large and small veins that communicate freely with the dorsal veins. The penile skin and subcutaneous tissue are drained by superficial dorsal veins, which then empty into the saphenous veins.

Activation of the cavernous autonomic nerves produces a full erection secondary to filling and trapping of blood in the cavernous bodies. After full erection is achieved, contraction of the ischiocavernosus muscle (from activation of the somatic nerves) compresses the proximal corpora and raises the intracorporal pressure well above the systolic blood pressure, resulting in rigid erection (Table 39–1). This rigid phase occurs naturally during masturbation or sexual intercourse but can also occur from slight bending of the penis, without muscular action. The erection process can be divided into phases as shown in Table 39–1 and Figure 39–2. The hemodynamics of the penile glans is somewhat different. Arterial flow increases in much the same manner as that in the shaft. Because it lacks the tunica albuginea, however, the glans functions as an arteriovenous fistula during the full erection phase. Nevertheless, during rigid erection, most of the venous channels are temporarily compressed, and further engorgement of the glans can be observed (Lue, 2999).

▶ Mechanism of Penile Erection

The penile erectile tissue, specifically cavernous, arteriolar, and arterial wall smooth musculature, is key to the erectile process. In the flaccid state, these smooth muscles are tonically contracted as a result of intrinsic smooth-muscle tone and possibly tonic adrenergic discharge, allowing only a small amount of arterial flow for nutritional purposes. The blood partial pressure of oxygen (PO_2) is ~35 mm Hg.

Table 39–1. Phases of the erection process.[a]

Flaccid phase (1)

Minimal arterial and venous flow; blood gas values equal those of venous blood.

Latent (filling) phase (2)

Increased flow in the cavernous artery during both systolic and diastolic phases. Decreased pressure in the internal pudendal artery; unchanged intracavernous pressure. Engorgement of the penis.

Tumescent phase (3)

Rising intracavernous pressure until full erection is achieved. Penis shows more expansion and elongation with pulsation. The arterial flow rate decreases as the pressure rises. When intracavernous pressure rises above diastolic pressure, flow occurs only in the systolic phases.

Full erection phase (4)

Intracavernous pressure can rise to as much as 80–90% of the systolic pressure.

Blood gas values approach those of arterial blood.

Rigid erection phase (5)

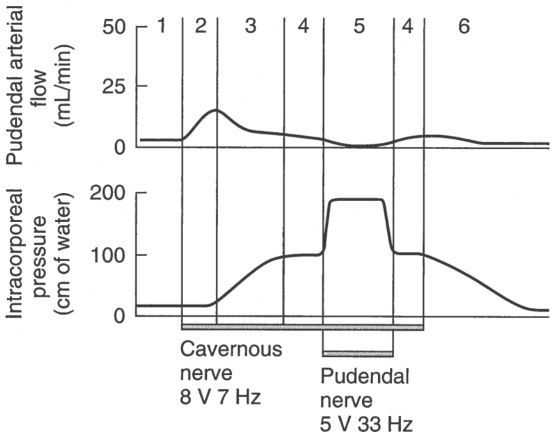
As a result of contraction of the ischiocavernosus muscle, the intracavernous pressure rises well above the systolic pressure, resulting in rigid erection. During this phase, almost no blood flows through the cavernous artery; however, the short duration prevents the development of ischemia or tissue damage.

Detumescent phase (6)

After ejaculation or cessation of erotic stimuli, sympathetic tonic discharge resumes, resulting in contraction of the smooth muscles around the sinusoids and arterioles. This diminishes the arterial flow to flaccid levels, expels a large portion of blood from the sinusoidal spaces, and reopens the venous channels. The penis returns to its flaccid length and girth.

[a] Numbers 1–6 correspond to phases shown in Figure 39–2.

When smooth muscles relax following the release of neurotransmitters, resistance to incoming flow drops to a minimum. Arterial and arteriolar vasodilatation occurs, and sinusoids expand to receive a large increase of flow. Trapping of blood causes the penis to lengthen and widen until the capacity of the tunica albuginea is reached. Expansion of the sinusoidal walls against the tunica albuginea results in compression of the subtunical venous plexus. In addition, uneven stretching of the layers of the tunica albuginea compresses the emissary veins and effectively reduces the venous flow to a minimum (Lue, 2000) (Figure 39–3A,B). Intracavernous pressure (ICP) and PO_2 increase to approximately 100 and 90 mm Hg, respectively, raising the penis from a dependent position to the erect state; further pressure increases (to several hundred millimeters of mercury) in response to contraction of the ischiocavernosus muscles, resulting in the rigid erection phase (Dean and Lue, 2005; Gratzke et al, 2010).



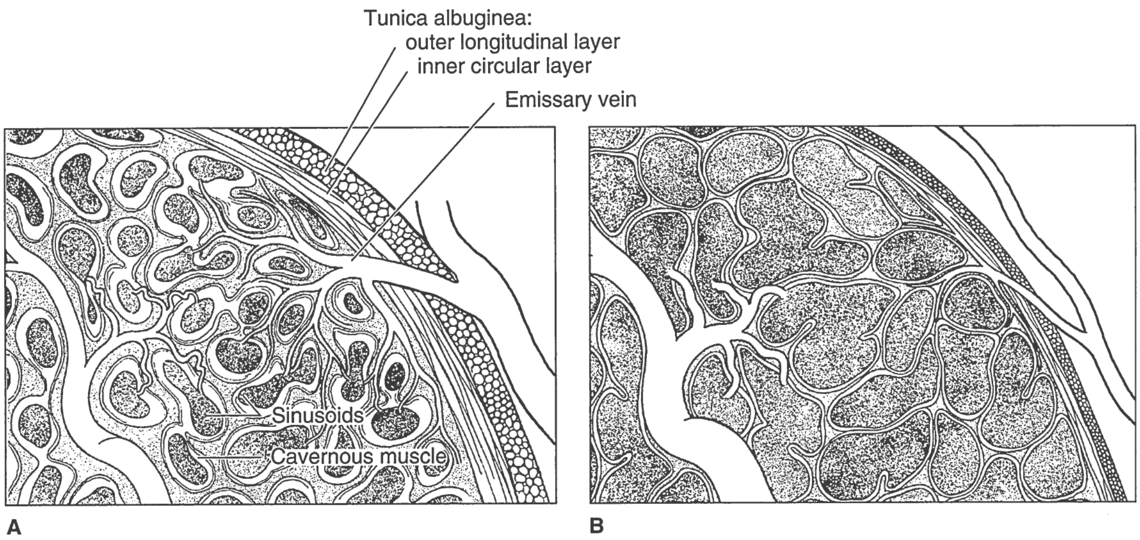
▲ **Figure 39–2.** Phases of penile erection (induced in monkeys via neurostimulation). Numbers correspond to phases outlined in Table 37–1. (Lower tracing = intracavernous pressure; upper tracing = flow within the internal pudendal artery.)

Hormones and Sexual Function

Androgens are essential for male sexual maturity. Testosterone (T) regulates gonadotropin secretion and muscle development; dihydrotestosterone mediates male sexual maturation, including hair growth, acne, male pattern baldness, and spermatogenesis. In adults, androgen deficiency results in decreased libido (sexual interest) and decreased seminal volume. Aging is associated with a progressive decline of T, dehydroepiandrosterone, thyroxine, melatonin, and growth hormone, and with increased levels of sex hormone–binding globulin, pituitary gonadotropins, and prolactin (Morales, 2005). In a longitudinal study of middle-aged men for 7–10 years, total T levels declined at 0.8% per each year of age, whereas both free and albumin-bound T declined at about 2% per year. Sex hormone–binding globulin increased at 1.6% per year (Feldman et al, 2002). Testosterone levels do not correspond to severity of ED; however, lower T levels are observed in men with reduced libido. Although frequency, magnitude, and latency of nocturnal penile erections are reduced with decreased T, erectile response to visual sexual stimulation is preserved in men with hypogonadism, suggesting that androgen is not essential for erection. Because of the inhibitory action of prolactin on central dopaminergic activity and resultant decreases in gonadotropin-releasing hormone secretion, hyperprolactinemia of any cause results in both reproductive and sexual dysfunction (Corona et al, 2004).

Neurotransmitters and Pharmacology of Erection

Neural control of penile erection involves adrenergic, cholinergic, and nonadrenergic–noncholinergic (NANC) neuroeffector systems. Adrenergic nerves mediate intracavernous



▲ **Figure 39–3.** The mechanism of penile erection. In the flaccid state *(**A**)*, the arteries, arterioles, and sinusoids are contracted. The intersinusoidal and subtunical venular plexuses are wide open, with free flow to the emissary veins. In the erect state *(**B**)*, the muscles of the sinusoidal wall and the arterioles relax, allowing maximal flow to the compliant sinusoidal spaces. Most of the venules are compressed between the expanding sinusoids. Even the larger intermediary venules are sandwiched and flattened by distended sinusoids and the noncompliant tunica albuginea. This effectively reduces the venous capacity to a minimum.

smooth-muscle contraction, maintaining the penis in a nonerect state. Currently, it is suggested that sympathetic contraction is mediated by activation of postsynaptic α_{1a}- and α_{1d}-adrenergic receptors and modulated by presynaptic α_2-adrenergic receptors (Giuliano, 2006). Cholinergic nerves may contribute to smooth-muscle relaxation and penile erection through inhibition of adrenergic nerves via inhibitory interneurons and the release of nitric oxide (NO) from the endothelium by acetylcholine (Saenz de Tejada et al, 2004).

The principal neurotransmitter for penile erection is NO from parasympathetic, NANC nerve terminals. Once blood rushes into the sinusoids, shear stress can also release NO from endothelium to augment smooth-muscle relaxation and erection. In addition, oxygen tension and substances secreted by endothelial cells lining the sinusoidal spaces, prostaglandins, endothelin, and angiotensin may also be involved in penile erection and detumescence (Musicki and Burnett, 2006). The agents capable of inducing erection and causing detumescence are summarized in Table 39–2. Although action mechanisms vary, erection-inducing substances cause smooth muscle to relax and detumescence-inducing agents cause them to contract.

▶ Molecular Mechanism of Smooth-Muscle Contraction and Relaxation

Smooth-muscle contraction is regulated by Ca^{2+}. As cytosolic free Ca^{2+} increases from resting levels of 120–270 to 500–700 nM, calmodulin-4 Ca^{2+} complex binds to myosin light-chain kinase. The activated kinase then phosphorylates the light chain and initiates a contraction cycle (Gratzke et al, 2010). Once cytosolic Ca^{2+} returns to basal levels, calcium-sensitizing pathways take over. This pathway involves rho-A, a small monomeric G protein that activates rho-kinase. Activated rho-kinase phosphorylates, and thereby inhibits, the regulatory subunit of smooth-muscle myosin

Table 39–2. Agents reported to induce or inhibit penile erection.

Inducers	Inhibitors
Papaverine	Phenylephrine
Phentolamine	Epinephrine
Phenoxybenzamine	Norepinephrine
Alprostadil (prostaglandin E1)	Metaraminol
Vasoactive intestinal polypeptide (VIP)	Ephedrine
Calcitonin gene-related peptide (CGRP)	Prostaglandin I2
Nitric oxide donor	Prostaglandin $F_{2\alpha}$
Guanylate cyclase activator	Thromboxane A2 (TXA2),
Phosphodiesterase inhibitors	Endothelin
Rho-kinase inhibitors	Angiotensin II

phosphatase, preventing dephosphorylation of myofilaments and maintaining contractile tone (Jin and Burnett, 2006). The emerging consensus is that phasic contraction of penile smooth muscle is regulated by increased cytosolic Ca^{2+} and tonic contraction is governed by calcium-sensitizing pathways.

Signal Transduction in Penile Erection

During sexual stimulation, NO released from nerve endings and endothelium diffuses into the trabecular and arterial smooth-muscle cells to activate guanylyl cyclase, catalyzing the formation of second messenger cyclic guanosine monophosphate (cGMP). cGMP, in turn, activates protein kinase G, phosphorylating potassium and calcium channels; the result is hyperpolarization, reduced intracytosolic calcium, and dissociation of the myosin head from actin as smooth muscle relaxes. Cyclic adenosine monophosphate (cAMP) is another second messenger involved in smooth-muscle relaxation and is activated by cAMP-signaling molecules including adenosine, calcitonin gene-related peptides, and prostaglandins (Lin et al, 2005).

These second messengers activate cAMP- and cGMP-dependent protein kinases, resulting in a drop of cytosolic free calcium and smooth-muscle relaxation via the (1) opening of the potassium channels and hyperpolarization, (2) sequestration of intracellular calcium by the endoplasmic reticulum, and (3) blockage of calcium influx through inhibition of voltage-dependent calcium channels (Dean and Lue, 2005). On the other hand, norepinephrine, phenylephrine, and endothelin appear to activate phospholipase C, leading to the formation of inositol triphosphate and diacylglycerol. The net result is increased cytoplasmic calcium and subsequent smooth-muscle contraction. Detumescence occurs following degradation of cGMP and cAMP to GMP and AMP, respectively, by specific types of phosphodiesterase. Eleven classes of phosphodiesterase have been identified. The penis is rich in phosphodiesterase type 5 (GMP-specific), and therefore the selective type 5 phosphodiesterase inhibitors (avanafil, sildenafil, tadalafil, and vardenafil) can improve penile erections in patients with ED.

SEXUAL DYSFUNCTION IN HUMAN MALES

Male sexual dysfunction, denoting the inability to achieve a satisfactory sexual relationship, may involve inadequacy of erection or problems with emission, ejaculation, or orgasm. The following terms are relevant in this context:

Premature (rapid) ejaculation refers to persistent or recurrent occurrence of ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it.

Retarded ejaculation is undue delay in reaching a climax during sexual activity.

Retrograde ejaculation denotes backflow of semen into the bladder during ejaculation owing to an incompetent bladder neck mechanism.

Anorgasmia is the inability to achieve an orgasm during conscious sexual activity, although nocturnal emission may occur.

EPIDEMIOLOGY

In the Massachusetts Male Aging Study, a community-based survey of men between 40 and 70 years of age, representing 52% of respondents, reported some degree of erectile dysfunction (ED): 17% mild, 25% moderate, and 10% complete. Although the prevalence of mild ED remained constant (17%) between the ages of 40 and 70 years, there was a doubling in the number of men reporting moderate ED (from 17% to 34%) and a tripling in the number of men reporting complete ED (from 5% to 15%) (Feldman et al, 2004). More than 70% of men aged >65 years report that they are sexually active; however, 40% are dissatisfied with their sexual function (Braun et al, 2000). Among the major predictors of ED are hypertension, hyperlipidemia, diabetes mellitus, and heart disease. Risk of ED appears to increase with smoking, and may occur in a dose-dependent manner (Polsky et al, 2005). There is a higher prevalence of ED in men who have undergone radiation or surgery for prostate cancer or other pelvic malignancies. The psychological correlates of ED include decreased self-esteem, depression, anxiety, anger, and relationship dissatisfaction Althof et al, 2006). Other male sexual dysfunctions have also been found to be highly prevalent; premature ejaculation and decreased libido (lack of sexual interest) are common patients' concerns.

Classification and Pathogenesis

The classification system of ED most commonly used encompasses organic, psychogenic, and mixed etiologies of ED and is endorsed by the International Society of Impotence Research (Table 39–3). In the 1950s, 90% of cases of ED were believed to be psychogenic. Most authors now believe that mixed ED is the most common.

Psychological Disorders

Many psychological conditions (performance anxiety, strained relationship, lack of sexual arousal, depression, and schizophrenia) can either cause or aggravate ED. Sexual behavior and penile erections are controlled by the hypothalamus, cerebral cortex, and limbic systems. Given the number and complexity of known and unidentified factors involved, it is not surprising that the pathogenesis of psychogenic ED is still speculative. Possible mechanisms

Table 39–3. Classification of ED recommended by the International Society for Sexual Medicine.

- **Psychogenic**
  - Generalized type
    - Generalized unresponsiveness
      - Primary lack of sexual arousability
      - Aging-related decline in sexual arousability
    - Generalized inhibition
      - Chronic disorder of sexual intimacy
  - Situational type
    - Partner-related
      - Lack of arousability in specific relationship
      - Lack of arousability due to sexual object preference
      - High central inhibition due to partner conflict or threat
    - Performance-related
      - Associated with other sexual dysfunction/s (eg, rapid ejaculation)
      - Situational performance anxiety (eg, fear of failure)
    - Psychological distress or adjustment-related
      - Associated with negative mood state (eg, depression) or major life stress (eg, death of partner)
- **Organic**
  - Neurogenic
  - Hormonal
  - Arterial
  - Cavernosal (venogenic)
  - Drug-induced
- **Mixed organic/psychogenic (most common type)**

proposed include an imbalance of central neurotransmitters, overinhibition of spinal erection center by the brain, inadequate NO release, and s pathetic overactivity (Bodie et al, 2003).

Neurogenic Disorders

It has been estimated that up to 20% of all ED is neurogenic in origin, resulting from peripheral (cavernous and pudendal nerve) or central pathologies. In men with spinal cord injury, the degree of erectile function depends on the nature, location, and extent of the lesion. Brain lesions associated with ED include dementias, Parkinson's disease, stroke, tumors, trauma, and Shy–Drager syndrome (Papatsoris et al, 2006). Peripheral neuropathy due to diabetes mellitus, chronic alcohol abuse, or vitamin deficiency may affect the nerve endings and result in a deficiency of neurotransmitters. Direct injury to the cavernous or pudendal nerves from trauma, radical pelvic surgeries for malignancy, or pelvic irradiation can also cause ED. It is important to note that even with nerve-sparing approaches to prostatic and rectal surgery, erectile recovery can take up to 24 months or longer.

Hormonal Disorders

Recent data reveal a significant increase of hypogonadism with age. Hypogonadism due to hypothalamic or pituitary tumors, estrogen or antiandrogen therapy, or orchiectomy can suppress sexual interest and nocturnal erections. Hyperprolactinemia, Cushing's syndrome, and Addison's disease can cause decreased libido and ED. Hyperthyroidism is commonly associated with decreased libido, likely due to elevated estrogen levels, while hypothyroidism can contribute to ED through diminished testosterone secretion and elevated prolactin levels (Veronelli et al, 2006).

Arterial Disorders

Although arteriogenic ED may be congenital or due to trauma, most often it is part of a generalized systemic arterial disease. Traumatic arterial occlusive or atherosclerotic disease of the hypogastric (iliac)–pudendal–cavernous arterial tree can decrease flow to the sinusoidal spaces and perfusion pressure, thus decreasing the rigidity or prolonging time to maximal erection. Some patients with severe arterial disease may retain erectile function as long as arterial flow exceeds venous flow; conversely, some patients with minimal arterial disease may develop partial or complete ED because of large venous outflow, cavernous smooth-muscle dysfunction, or inadequate neurotransmitter release (Dean and Lue, 2005).

High prevalence of ED has been reported in men with coronary, cerebral, and peripheral vascular diseases (Kloner et al, 2003; Chai et al, 2009). Among men with coronary arterial disease, the prevalence of ED increases as the severity of coronary arterial lesions increases. In patients with chronic coronary disease who also had ED, onset of sexual dysfunction occurred before CAD onset in 93%, with a mean time interval of 24 [12–36] months (Montorsi et al, 2006). When ED occurs in a younger man, it is associated with a marked increase in the risk of future cardiac events, whereas in older men, ED appears to be of little prognostic importance (Inman et al, 2006).

Common risk factors associated with arterial insufficiency include hypertension, hyperlipidemia, diabetes mellitus, and metabolic syndrome. Long-distance cycling is also a likely risk factor for vasculogenic and neurogenic ED (Huang et al, 2005).

Cavernosal Disorders

Cavernous veno-occlusive dysfunction (CVOD) may result from a variety of pathophysiologic processes. Degenerative changes (Peyronie's disease, aging, and diabetes) and traumatic injury to the tunica albuginea (penile fracture) can impair the compression of the subtunical and emissary veins. Fibroelastic alteration of the trabeculae, cavernous smooth muscle, and endothelium may result in venous leakage (Devechi et al, 2006). Men with diabetes mellitus and atherosclerosis are at increased risk of smooth-muscle atrophy, fibrous replacement, and endothelial disruption.

Medication-Induced Erectile Dysfunction

Many drugs have been reported to cause ED, although the mechanism of action is often unknown and there are few controlled studies on the sexual side effects of a specific agent. As ED is common among older men, it will coexist with other conditions that are themselves risk factors for ED, such as cardiovascular disease, diabetes, or depression. Sexual symptoms related to medications can also involve a combination of complaints concerning desire, arousal, and orgasm rather than being limited to impaired erection.

In general, drugs that interfere with central neuroendocrine or local neurovascular control of penile smooth muscle have the potential to cause ED. Central neurotransmitter pathways, including serotonergic, noradrenergic, and dopaminergic pathways involved in sexual function, may be disturbed by antipsychotics, antidepressants, and centrally acting antihypertensive drugs (Balon, 2005). Selective serotonin reuptake inhibitors are the most common class of drugs currently used to treat depression; it is estimated that up to 50% of patients using these agents experience a change in sexual function. Nonspecific β-adrenergic blocking drugs may cause ED by potentiating α_1-adrenergic activity in the penis. Conversely, α_1 blockers and angiotensin II–receptor blockers both tend to improve sexual function during treatment and may therefore be useful when commencing antihypertensive therapy in men with preexisting ED. Thiazide diuretics have been reported to cause ED; spironolactone can also cause a decrease in libido and gynecomastia. Other drugs thought to cause ED include opiates, antiretroviral agents, and histamine H_2 receptor antagonists (cimetidine). α-Adrenergic blocking drugs, such as doxazosin, terazosin, and tamsulosin, may cause retrograde ejaculation owing to relaxation of the bladder neck (Giuliano, 2006).

Antiandrogens modify sexual behavior by varying degrees, ranging from complete loss to normal function, chiefly by modulating sexual desire via central nervous system (CNS) androgen receptors. Finasteride, a 5-α-reductase inhibitor commonly used to treat benign prostatic hypertrophy, is the antiandrogen with the least effect on circulating testosterone and sexual function. Sexual symptoms are reported in approximately 5% of men treated with a 5-mg dose (Miner et al, 2006). Estrogens and drugs with antiandrogenic action such as ketoconazole, LHRH agonists nonsteroidal (bicalutamide) and steroidal (cyproterone acetate) acetate can diminish sexual function. The near-complete androgen deprivation achieved by medical castration with LHRH agonists results in a profound loss of sexual desire, which is usually accompanied by ED.

Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle and is seen to approximately double the rate of ED in coronary artery disease, hypertension, and atherosclerosis (Korenman, 2004). Alcohol in small amounts improves erection and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts can cause central sedation, decreased libido, and transient ED. Chronic alcoholism may cause hypogonadism and polyneuropathy, which may affect penile nerve function.

Aging and Systemic Disease

Sexual function progressively declines in “healthy” aging men. Longitudinal studies demonstrate a nonlinear decline for most aspects of sexual function as age increases, with a more pronounced decline in older groups (Araujo et al, 2004). The latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, ejaculatory volume decreases, and the refractory period between erections lengthens. There is also a decrease in penile sensitivity to tactile stimulation, a decrease in serum testosterone concentration, and an increase in cavernous muscle tone. While psychological and organic factors are important contributors to ED across age groups, organic issues tend to play a more profound role as men age.

Erectile dysfunction in men with diabetes mellitus (DM) occurs approximately threefold more frequently than that of the general population, and can be the presenting symptom for DM and/or predict later neurologic sequelae (Fonseca and Jawa, 2005). Diabetes may affect small vessels, cavernous nerve terminals, smooth muscle, and endothelial cells; neurovascular sequelae of long-term diabetes results in decreased responsiveness to oral PDE5 inhibitor therapy. Obesity, a component of metabolic syndrome, has been linked to endothelial dysfunction, androgen deficiency, and ED (Traish et al, 2009).

Men with severe pulmonary disease may have ED because of fear of aggravating dyspnea during sexual intercourse (Koseoglu et al, 2005). Patients with angina, myocardial infarction (MI), or heart failure may have ED from anxiety, depression, or concomitant penile arterial insufficiency, which is quite common in these patients. Chronic renal failure has frequently been associated with diminished erectile function, impaired libido, and infertility (Shamsa et al, 2005). In men with chronic renal failure and ED, many were found to have cavernous artery occlusive disease and veno-occlusive dysfunction. The mechanism is likely multifactorial: low serum testosterone concentration, diabetes mellitus, vascular insufficiency, multiple medications, autonomic and somatic neuropathy, and psychological stress. Other systemic disorders such as cirrhosis, chronic debilitation, and cachexia can cause ED due to loss of libido or neurovascular dysfunction.

DIAGNOSIS AND TREATMENT

The management of ED is built on a patient-centered and evidence-based principles. A detailed medical, sexual, and psychosocial history and a thorough physical examination are the most important steps in the differential diagnosis of sexual dysfunction. Interviewing the partner, if available, is helpful in eliciting a reliable history, planning treatment, and obtaining a successful outcome.

Medical, Sexual, and Psychosocial History

The goals of the medical history are to evaluate the potential role of underlying medical conditions, differentiate between organic and psychogenic causes, and assess the role of medication(s), both causative and therapeutic. The patient's past surgical history may similarly yield insights. A sexual history confirms the diagnosis and should ascertain the severity, onset, and duration of the problem, as well as the presence of concomitant medical or psychosocial factors. It is necessary to determine whether the presenting complaint (eg, ED, premature ejaculation) is the primary sexual problem or if some other aspects of the sexual response cycle (desire, ejaculation, orgasm) are involved. Psychosocial assessment of past and present partner relationships is essential given the interpersonal context of sexual problems. Sexual dysfunction may affect the patient's self-esteem and coping ability, as well as social relationships and occupational performance.

Physical and Laboratory Examination

A focused physical examination is performed on each patient, assessing the genitourinary, endocrine, neurologic, and vascular systems, and includes a complete genital examination, including digital rectal, and measurement of blood pressure and heart rate. Examination may yield a diagnosis of Peyronie's disease, prostatic enlargement, malignancy, or evidence of hypogonadism (decreased testes size, altered secondary sex characteristics).

Recommended tests include fasting glucose, lipid profile, and morning testosterone (calculated free testosterone is more reliable for establishing hypogonadism). Diabetics should undergo hemoglobin A1C measurement, and additional hormonal testing (prolactin, follicle-stimulating hormone [FSH], and luteinizing hormone [LH]) is required when low testosterone levels are noted or for clinical suspicion of abnormality. Optional tests, including prostate-specific antigen (PSA), thyroid-stimulating hormone (TSH), complete blood count, and creatinine, must be tailored to the patient's complaints and risk factors.

Self-Reported Questionnaires and Laboratory Investigations

The most commonly used validated questionnaires are the 15-item International Index of Erectile Function (IIEF) or an abridged 5-item version (IIEF-5) more suited for office use. Sexual domain functions measured by the IIEF include erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. These tools are useful to determine baseline erectile function and to assess the impact of a specific treatment modality. Classification of ED severity is divided into five categories based on the IIEF-5: severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25) (Rosen, 2004).

The physician should review the findings, inquire about the goals and preferences of the man (and his partner), and discuss further diagnostic and therapeutic options such that his (or their) participation in the decision-making process is well informed. For a minority of patients, referral for further testing and/or assessment may be appropriate. Indications for referral include patient request, treatment failure, complex gonadal or other endocrine disorders, neurologic deficits suggestive of brain or spinal cord disease, deep-seated psychological or psychiatric problems, and active cardiovascular disease. Patients deemed to be at intermediate or higher cardiac risk (cardiac status uncertain, moderate to severe symptoms, or inability to perform exercise of modest intensity) should be assessed by a cardiologist/internist and sexual activity deferred until cardiac condition is stabilized or resumption of sexual activity is deemed safe by the consultant. Low-risk patients, those able to perform exercise of modest intensity (6 or more metabolic equivalents [METs]) without symptoms, do not generally require cardiologic assessment (Jackson et al, 2006).

Advanced Testing for Erectile Dysfunction

For patients with more complex problems, including penile deformity, history of pelvic or perineal trauma, ED of unknown etiology, cases requiring vascular or neurosurgical intervention, complicated endocrinopathy, complicated psychiatric disorder, complex relationship problems, medicolegal concerns, or at the patient's request, various vascular and neurologic diagnostic tests are available to identify the cause of ED or plan treatment (Table 39–4).

A. Tests for Penile Vascular Function

The goal of vascular evaluation is to identify and evaluate arterial and veno-occlusive dysfunction. The most commonly utilized tests include combined injection and stimulation (CIS), duplex ultrasound, dynamic infusion cavernosometry and cavernosography (DICC), and selective penile angiography. A test for endothelium dependent flow mediated dilation of the brachial artery has been proposed but will not be discussed here because it is not specific for penile function (Yavuzgil et al, 2005).

1. Combined intracavernous injection–stimulation (CIS) test—This is a commonly performed diagnostic procedure for ED. It consists of an intracavernous injection, visual or manual sexual stimulation, and a rating of the subsequent

Table 39–4. Tests Suggested for Various Treatment Options.[a]

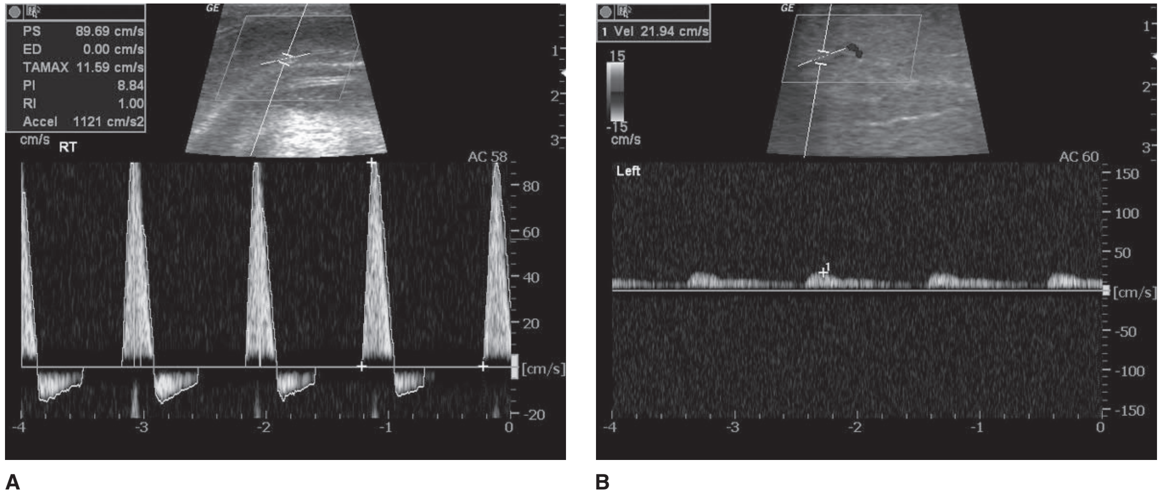
- **1. Oral medication, transurethral therapy, or vacuum constriction device**
  - No further testing
- **2. Intracavernous injection therapy**
  - CIS test
- **3. Penile prosthesis**
  - CIS test or NPT test or duplex scanning
- **4. Venous surgery**
  - CIS test
  - Duplex scanning or cavernous arterial occlusion pressure test
  - Cavernosometry and cavernosography
- **5. Arterial surgery (or combined arterial and venous surgery)**
  - CIS test
  - Duplex scanning or cavernous arterial occlusion pressure
  - Cavernosometry and cavernosography
  - Pharmacologic arteriography

CIS, combined injection and stimulation; NPT, nocturnal penile tumescence.

[a] Regardless of desired treatment, all patients must undergo history, physical examination, and basic laboratory testing.

erection. The most commonly used vasodilator is 10 μg of alprostadil or 0.3 mL of a mixture of papaverine and phentolamine. A rigid erection lasting > 10 minutes is indicative of normal venous function. However, the same conclusion cannot be applied for arterial function, as some men with mild arterial insufficiency can also have the same response. Although some researchers have modified this test by using an oral phospodiesterase V inhibitor and audiovisual sexual stimulation, the normal criteria have not been established.

2. Color duplex ultrasonography—Color duplex ultrasound is utilized when accurate vascular diagnostic testing is indicated. It consists of an intracavernous pharmaco-test and measurement of blood flow by color duplex ultrasound (Aversa and Sarteschi, 2007) (Figure 39–4). High-resolution (7–12-MHz) real-time ultrasonography and color pulsed Doppler enables the ultrasonographer to visualize the dorsal and cavernous arteries selectively and perform dynamic blood flow analysis, and is the best tool available for the diagnosis of high-flow priapism and localization of a ruptured artery. Normal arterial response is a peak flow velocity measured at the base of penis of >30 cm/s, a sharp upstroke of the waveform, and absence of diastolic flow after sexual stimulation. Ultrasound can also be used to detect penile abnormalities such as Peyronie's plaque, calcifications, thickened vessel walls, and intracavernous fibrosis. When the Doppler waveform exhibits high systolic flow (>30 cm/s peak systolic velocity [PSV]) and persistent end-diastolic flow velocity (EDV) > 5 cm/s accompanied by quick detumescence after self-stimulation, the patient is considered to have venogenic impotence. The parameters useful in diagnosing venous leakage include a diastolic venous flow velocity of >5 cm/s and/or a resistive index (RI) of <0.75. RI = peak systolic velocity (PSV) – EDV / PSV (Sikka et al, 2013).



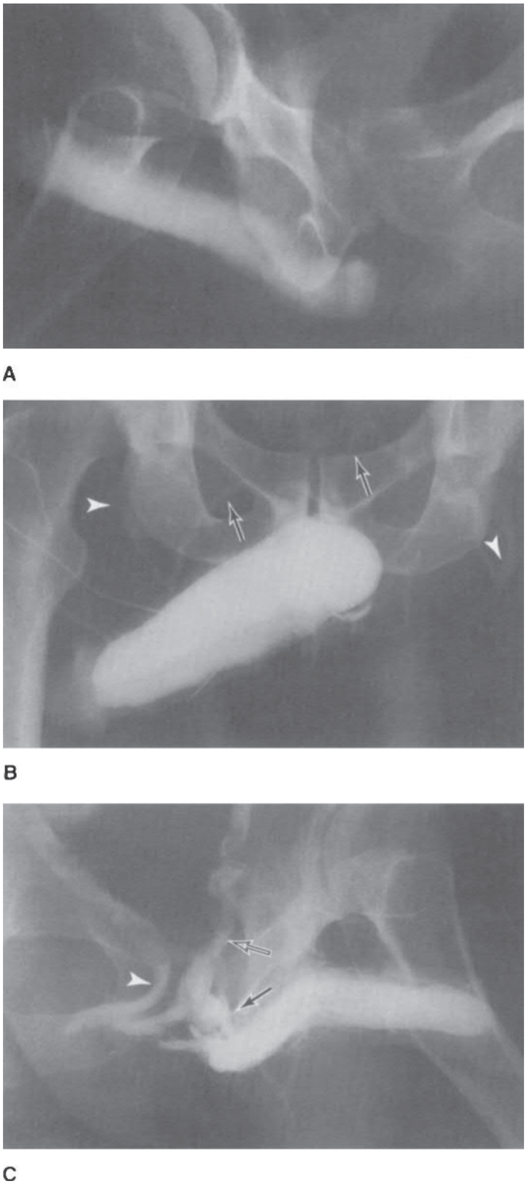
▲ **Figure 39–4.** Color duplex ultrasonography analysis of arterial response after intracavernous injection of a vasodilator. *(**A**)* Excellent arterial response in a healthy young man with psychogenic ED. The peak systolic (PS) flow velocity is 89.69 cm/sec, end-diastolic (ED) flow velocity is 0 cm/sec, and the resistance index is 1. There is a negative flow wave at the early diastolic phase indicative of a good erectile response and the intracavernous pressure is above the systemic diastolic pressure. *(**B**)* Poor arterial response in an older man with vasculogenic ED. The peak systolic velocity is 21.94 cm/sec indicative of penile arterial insufficiency.

3. Cavernosometry and cavernosography—Pharmacologic cavernosometry involves ICI of a potent vasodilator combination (papaverine + phentolamine + alprostadil) followed by saline infusion and simultaneous monitoring of ICP to assess the penile outflow system. In men with normal venous function, the maintenance flow should be <10 mL/min at an ICP of 100 mm Hg, and the rate at which ICP drops after infusion ceases should be <50 mm Hg in 30 seconds. Veno-occlusive dysfunction is indicated by either (1) the inability to increase ICP to the level of the mean systolic blood pressure with saline infusion or (2) a rapid drop of ICP after cessation of infusion.

Cavernosography is used to visualize the site of venous leakage. Following the induction of an artificial erection by ICI of vasodilators (activation of the veno-occlusive mechanism), diluted radiocontrast solution is infused into the corpora cavernosa (Mulhall et al, 2004). Minimal or no contrast is seen outside the corpora cavernosa with normal veno-occlusive function. In patients with venous leakage of congenital or traumatic origin, the leakage is seen most often in the crura or at the site of injury, respectively (Figure 39–5). Leakage sites to the glans, corpus spongiosum, superficial dorsal veins, and cavernous and crural veins can be detected. In most patients, more than one site is visualized. The typical finding in men with intrinsic disease of the corpus cavernosum or the tunica albuginea is a diffuse leakage through all penile venous channels (Glina and Ghanem, 2013).

4. Cavernous arterial occlusion pressure—Cavernous arterial occlusion pressure, a variation of penile blood pressure measurement, involves infusing saline solution into the corpora after ICI of vasodilators to raise the ICP above the systolic blood pressure. A pencil Doppler transducer is then applied to the side of the penile base, saline infusion is stopped, and the intracavernous pressure is allowed to fall. The pressure at which the cavernous arterial flow becomes detectable is defined as the **cavernous artery systolic occlusion pressure (CASOP)**. A gradient between the cavernous and brachial artery pressures of <35 mm Hg and equal pressure between the right and left cavernous arteries are defined as normal.

5. Arteriography—Arteriography is reserved for evaluation of the complex patient for whom revascularization surgery is contemplated; indications include the young patient with ED secondary to a traumatic arterial disruption or a patient with a history of perineal compression injury. The study is performed by ICI of a vasodilating agent (papaverine, papaverine + phentolamine, or alprostadil) followed by selective cannulation of the internal pudendal artery and injection of a diluted contrast solution of low osmolarity. The anatomy and radiographic appearance of the cavernous arteries is then evaluated, as are the iliac vessels, dorsal penile arteries, and the size and length of the inferior epigastric arteries.



▲ Figure 39–5. Cavernosography after intracavernous injection of papaverine. In a normal man *(**A**)*, the cavernosogram shows opacification of the erect corpora cavernosa and nonvisualization of penile veins. In image *(**B**)*, the patient has a large leak through both superficial dorsal veins (*arrows*) to the saphenous veins (*arrowheads*). Film *(**C**)* shows abnormal venous drainage via the cavernous veins (*solid arrow*) into the preprostatic plexus (open arrow) and the internal pudendal veins (*arrowhead*). (Reproduced with permission from Lue TF, Tanagho EA: Physiology of erection and pharmacological management of impotence, J Urol. 1987 May;137(5):829–836.)

B. Neurologic Tests

The effect of a neurologic deficit on penile erection is a complicated phenomenon and with few exceptions, neurologic testing rarely changes management. Testing is recommended for specific research protocols or medicolegal investigations, including cases of trauma or surgical complications, or it can be used in selected cases to determine whether a referral to a neurologist is necessary (eg, workup for possible spinal cord tumor).

Somatic nerves are evaluated by testing nerve conduction velocities and evoked potentials, and these tests have well-known reproducibility and validity. Autonomic function tests are less reliable because they simultaneously measure a chain of events or reactions involving receptors, small fibers, and target organs. The complex interactions among central and peripheral sympathetic and parasympathetic nerve systems make autonomic testing difficult. Currently available tests are not well standardized, and lack validity, reproducibility, and comparability.

A common test performed in the urologist's office is biothesiometry. This test is designed to measure the sensory perception threshold to various amplitudes of vibratory stimulation produced by a handheld electromagnetic device (biothesiometer) placed on the pulp of the index fingers, big toes, both sides of the penile shaft, and the glans penis. Penile thermal sensory testing may be performed to quantify conductance of small sensory nerve fibers, which can indirectly reflect autonomic disturbances in the context of diffuse neuropathies, such as diabetic polyneuropathy.

C. Nocturnal Penile Tumescence Test

Nocturnal erections, 80% of which occur during REM sleep, occur in healthy males of all ages and are relatively free of psychologically mediated effects. The average man has three to five episodes of nocturnal penile tumescence (NPT) each night, with episodes ranging from 30 to 60 minutes. Total NPT time declines with increasing age. Classically, Nocturnal penile tumescence has been measured by several methods, including the stamp test, snap or strain gauges, and sleep lab NPTR. Contemporary NPT testing is performed with simpler outpatient devices such as Rigiscan NPTR (Rigiscan, GOTOP Medical; St. Paul, MN). These devices electronically record the number, duration, rigidity, and circumference of penile erections. NPT was originally designed to differentiate psychogenic from organic ED, as a full erection indicates a functionally intact neurovascular axis. In the United States, it is now used mostly in medicolegal or complicated cases, as well as for research purposes.

D. Psychological Evaluation

Clinical subtypes of psychogenic ED include generalized versus situational and lifelong (primary) versus acquired (secondary, including substance abuse or major psychiatric illness). The psychological and interpersonal dimensions of sexual function and dysfunction are complex; therefore, a skillful diagnostic interview is the mainstay of a good psychological evaluation. A suggestive history of psychogenic ED includes sudden onset, selective dysfunction (eg, rigid erection with one partner and poor erection with others, or normal erection during masturbation or fantasy but not during intercourse), and a normal pattern of nocturnal erections coupled with an abnormal pattern during waking hours. This is often associated with anxiety, guilt, fear, emotional stress, and religious or parental inhibition. If the medical and sexual histories suggest a combination of organic and psychological risk factors, these patients should be diagnosed as having mixed organic/psychogenic ED; successful treatment must address both components. Although psychological consultation is not indicated for all patients, it is very useful in evaluating and treating men with deep-seated psychological problems.

NONSURGICAL TREATMENT OF ERECTILE DYSFUNCTION

Advances in pharmacologic therapy for ED have resulted in greater numbers of patients seeking primary and specialty care for sexual concerns. Oral phosphodiesterase type 5 inhibitors have emerged as the preferred first-line treatment of ED worldwide because of their efficacy, ease of use, and patient safety. Prior to their release, options were limited to lifestyle modification, medication changes, psychosexual therapy, vacuum devices, intraurethral agents, intracavernosal injection therapy, or penile prosthesis insertion.

▶ Lifestyle Changes

The beneficial effect of lifestyle change (total body weight loss of ≥10% by reducing caloric intake and increasing physical activity) was demonstrated in a randomized, single-blinded trial of 110 obese men (body mass index ≥ 30) age 35–55 years, without diabetes, hypertension, or hyperlipidemia, but with ED (a score of 21 or less on the IIEF). The beneficial effect was reproduced in a larger study of 209 nonobese men randomly assigned to an interventional versus a control group (Esposito et al, 2009).

It is well known that ED is intimately related to the atherosclerotic coronary and peripheral vascular diseases, as well as the metabolic syndrome, characterized by central obesity, abnormal lipids, insulin dysregulation, and borderline hypertension. Regular exercise, a healthy diet, smoking abstinence or cessation, and limiting the use of alcohol can reduce the risk of ED or improve underlying dysfunction. A Mediterranean-style diet (fruits, vegetables, nuts, whole grain, olive oil, and decreased saturated lipids) has been shown to improve endothelial function scores and inflammatory markers (C-reactive protein) when compared to men on a control diet (Esposito et al, 2010). Obesity and smoking have been prospectively identified as risk factors for ED, while physical activity is inversely associated with the development of ED.

Perineal compression on penile arteries from long-distance cycling may also represent a modifiable risk factor for ED. Changing the bicycle seat or riding practices will often improve erectile function if penile vascular compromise is identified; specific strategies include replacing a protruding nose with a noseless seat, changing posture to a more upright/reclining position, using a gel saddle, and tilting the seat downward (Huang et al, 2005).

Changing Medications

When a patient complains of sexual dysfunction after taking a certain medication, it is important to determine whether the problem is related to loss of sexual drive, impaired erection, or rapid/delayed ejaculation. In many situations, changing the medication to a different class of agents is a feasible first step. Antihypertensive agents therapeutically lower blood pressure; this primary effect has long been considered as the mechanism of their adverse actions on erection. Switching patients to agents such as α-adrenoceptor antagonists, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors may reverse ED in some patients. Patients complaining of sexual dysfunction while taking antidepressants may benefit from substitution (bupropion, nefazodone, buspirone, mirtazapine), drug holidays, selective serotonin reuptake inhibitors (SSRIs), dosage reduction, and/or PDE5 inhibitors.

Psychosexual Therapy

Therapies such as a phosphodiesterase-5 inhibitors or ICIs may provide more rapid relief for patients with ED compared to a prolonged course of psychosexual therapy. However, in patients with evidence of psychological problems, referral to a psychologist or sex therapist is highly recommended because the elimination of a specific underlying cause may result in a cure. Recent approaches to sex therapy have included cognitive-behavioral interventions focused on challenging or correcting maladaptive cognitions, behavioral techniques (desensitization and assertiveness exercises), exploration of past developmental experiences on present behavior, and couples therapy. Moreover, in some patients with mixed psychogenic and organic ED, psychosexual therapy may help relieve the anxiety and remove unrealistic expectations associated with medical or surgical therapy.

Hormonal Therapy

Referral to an endocrinologist is recommended for patients with thyroid, adrenal, pituitary, or hypothalamic dysfunction. In patients with hyperprolactinemia with or without hypogonadism, androgen therapy does not improve sexual function. Treatment should first be aimed at eliminating the offending drugs, such as estrogens, sedatives, neuroleptics, or morphine. Bromocriptine, a dopamine agonist that lowers prolactin levels and restores testosterone to normal, is used to reduce the size of prolactin-secreting adenomas. Surgical ablation may occasionally be required if the bromocriptine response is unsatisfactory or if visual field changes secondary to optic nerve compression occur.

Aging men with ED may show a variety of symptoms when hypogonadism coexists: low libido, depression, decreased intellectual abilities, lean body mass, bone mineral density, skin turgor, changes in body hair distribution, changes in sleep patterns, and increased visceral fat (Snyder et al, 2016). In the patient with documented hypogonadism and ED, it is reasonable to initiate androgen therapy; for hypogonadal patients unresponsive to PDE5 inhibitor therapy alone, the addition of testosterone may enhance the treatment effect and improve erectile function (Morales, 2005).

Parenteral depo-preparations of testosterone (T), such as testosterone cypionate and enanthate, are the least expensive form of androgen supplementation and are effective in restoring serum levels to normal. They are administered through deep intramuscular injection (200–250 mg q 2 weeks) and result in supraphysiologic levels of T for 72 hours with steady exponential decline to subphysiologic levels in 10–12 days. The initial supraphysiologic "rush" may be disconcerting to some patients, but others enjoy an improved sense of well-being, aggression, and libido. Also available are extra-long acting intramuscular injectable testosterone preparations that last approximately 10 weeks as well as testosterone pellets that last for 3–4 months. These include testosterone undecanoate, Nebido (not available in the USA, dosed with 1,000 mg initial dose followed by 1,000 mg dose at 6 weeks then again every 10–14 weeks), Aveed (available in the USA, the recommended doses are 750 mg initially, at 4 weeks, and then 750 mg every 10 weeks), and TESTOPEL pellets that are implanted subcutaneously with a trocar every 3–4 months. These long-acting formulations have been linked to injection-associated rare pulmonary oil microembolism and pellets implant site infection and extrusion.

Transdermal T delivery more closely simulates normal circadian levels of T if the patient applies the medication in the morning, as the higher initial absorption mimics normal diurnal variations. Several US Food and Drug Administration (FDA)-approved preparations are available in the United States. Testoderm TTS, which has largely replaced the Testoderm scrotal patch, is convenient to use as it is applied daily to the arm, back, or upper buttocks as a 5-mg patch. Another product, Androderm, comes as a patch that delivers 2.5 or 5 mg T per day. The most common adverse reactions to both are itching, chronic skin irritation, and allergic contact dermatitis. Patients should alternate application sites and avoid sun-exposed areas. Local application of cortisone cream may relieve irritated skin. AndroGel is a 1% gel pack (containing 50 mg, 75 mg, or 100 mg of T), which is also applied daily in the morning to clean, dry skin over the shoulders, upper arms, or abdomen. Hands should be washed thoroughly after application, as skin contact can transmit testosterone. Testim topical gel also contains 1% T, providing continuous transdermal delivery for 24 hours after a single application to intact, clean, dry skin of the shoulders and upper arms. One 5-g tube of Testim contains 50 mg of testosterone. Other topical gels include Testogel (50 mg in 5 gm packet), Fortesta 2% gel (metered dose pump –10 mg per actuation), Axiron 2% solution (metered dose pump –30 mg per actuation), and Tostran 2% gel (metered dose pump –10 mg per actuation).

When taken orally, methyl testosterone preparations are largely rendered metabolically inactive during "first pass" circulation through the liver. The large dosages (exceeding 200 mg/day) required to achieve therapeutic levels can be hepatotoxic, leading to hepatitis, cholestatic jaundice, hepatomas, hemorrhagic liver cysts, and hepatocarcinoma. Although unavailable in the United States, the only orally active and safe form of T is Andriol (testosterone–undecanoate in oleic acid [TU]), which, owing to its lipophilic side chain, is partly taken up by the lymph and partially escapes hepatic inactivation. The maximal plasma concentration is generally observed within 2–3 hours, but after 6–8 hours levels will have returned to pretreatment values. A dosage of 40 mg three times a day generally provides adequate androgen replacement, yielding T levels within the (low) normal range, whereas DHT levels are moderately increased (2–4 nmol/L). Absorption varies with food consumption, and the dosage should be based on plasma levels and clinical effects. Other FDA-approved delivery systems include Testopel subcutaneous pellets (dosage of two to six pellets [150–450 mg T]) that last for 4–6 months and Striant, a tablet-like mucoadhesive buccal system used to deliver 30 mg of T twice daily.

Potential Adverse Effects of Testosterone Replacement

Testosterone replacement is clearly the treatment of choice for hypogonadal men without contraindications. However, the potential risks of androgen therapy may outweigh the benefits for some patients. Supraphysiologic levels of T suppress LH and FSH production and can lead to infertility, breast tenderness, and gynecomastia. Erythrocytosis is the most common laboratory alteration noted with long-term therapy; increases in red cell mass, thromboxane A2, and platelet aggregation may increase cardiovascular risk. Androgens may also induce or worsen sleep apnea. Long-term therapy requires a commitment from the patient and the specialist for continued follow-up, as outlined below.

Regarding prostate safety, numerous studies available in the literature suggest that androgen replacement does not induce prostate cancer in men with normal prostates, and that placebo-controlled studies show little difference in prostate volume, PSA, and obstructive symptoms. No increased risk of prostate cancer has been noted in clinical trials of T supplementation, longitudinal population-based studies, or a high-risk population of hypogonadal men receiving T treatment (Morgentaler, 2006; Fernandes-Balsells et al, 2010).

When a patient desires T replacement, a digital rectal examination and a serum PSA level should be obtained. When in doubt, prostate imaging and/or biopsy may be performed before T therapy is provided. The presence of untreated prostate or breast cancer is an absolute contraindication to androgen supplementation. Patients without a cancer diagnosis should have a rectal examination and serum PSA 3 months and 6 months after initiating T replacement therapy and once a year thereafter according to standard of care. Laboratory surveillance should also include hemoglobin/hematocrit levels, liver function tests, cholesterol, and lipid profile. The efficacy of supplementation is determined by clinical response rather than blood levels of testosterone.

If a patient has a history of treated prostate cancer and hypogonadism, he may be a candidate for T replacement only after a prudent interval if there is no clinical or laboratory evidence of residual cancer. As long-term outcome data are not available, clinicians must exercise good clinical judgment together with adequate knowledge of advantages and drawbacks of T therapy in this situation. The risks and benefits must be clearly discussed with and understood by the patient, and the follow-up must be especially careful (Wang et al, 2009). A PSA should be obtained prior to starting treatment and 1 month afterward and then again at 6-month intervals, or if the patient is stable, consider annual PSAs.

The purported increased risk of cardiovascular disease (CVD) in response to T therapy remains largely unsubstantiated. In fact, some have suggested that T therapy may even be cardioprotective. Growing evidence available in the literature indicates that T therapy lowers CV risk rather than increasing harm (Morgentaler, 2016; Morgentaler et al, 2015). Nonetheless, it is recommended that the clinician thoroughly discuss all benefits and risks with the patient prior to commencing with a T replacement therapy plan, which should be individualized and based on patient-specific medical history and concerns.

Oral Pharmacologic Therapy

A. Phosphodiesterase (PDE) Inhibitors

Sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis), and avanafil (Stendra), the four selective phosphodiesterase-5 inhibitors (PDE5Is) currently approved for clinical use in the United States, have become the preferred first-line therapy for most men with ED because of their efficacy, safety, and ease of use. All are highly effective in enhancing erectile function across a wide range of outcome measures, causes of ED, patient subgroups, and regional populations. The four PDE5Is appear to have equivalent efficacy in the treatment of ED, are generally well tolerated, and have similar contraindications and warnings (Carson and Lue, 2005).

1. Mechanism of action—Sexual stimulation results in the release of NO from nerve endings and vascular endothelial cells in the penis. NO then diffuses into vascular and cavernous smooth muscle cells of the corpus cavernosum. Stimulation of guanylyl cyclase by NO elevates levels of cGMP, lowering cytoplasmic calcium and resulting in smooth muscle relaxation and subsequent penile erection. PDE-5Is amplify the NO-cyclic cGMP pathway through competitive inhibition of cGMP degradation by type 5 phosphodiesterase. Without sexual stimulation and resultant NO release, however, these inhibitors are ineffective.

2. Clinical efficacy—The clinical efficacy and safety of sildenafil, vardenafil, tadalafil, and avanafil has been evaluated in many placebo-controlled, double-blinded trials and open-label studies (Carson and Lue, 2005; Brock et al, 2002; Porst et al, 2003; Goldstein et al, 1998, 2012). Treatment effect was principally assessed by items 3 and 4 of the IIEF-15 questionnaire (ability to attain and maintain erection, respectively). For sildenafil, improvements in erectile function were reported by 56–84% of subjects taking 25–100 mg of sildenafil versus 25% in the placebo group. Little ED benefit and considerably more side effects were noted above 100 mg. For specific etiologies, sildenafil was effective in 70% of hypertensive patients, 57% of diabetics, 43% of radical prostatectomy patients, and 80% of spinal cord injury patients. The efficacy of vardenafil was similarly evaluated with 10- and 20-mg doses. Mean IIEF scores increased from 12.8 at baseline to 21 at week 12 of treatment (compared to an increase from 13.6 to 15.0 for placebo). Similarly, integrated phase III studies of tadalafil involving 1112 patients demonstrated IIEF erectile domain scores of 24 in men receiving a 20-mg dose versus 15 mg for placebo. More than 70% of intercourse attempts were successfully completed from >30 minutes to 36 hours after dosing. For difficult to treat groups, including diabetics, severe ED, and postradical prostatectomy, the four PDE5Is represent effective therapies for many men.

3. Time of onset—The onset of activity, in reports with similar methods, is 14 minutes with sildenafil, 10 minutes with vardenafil, 16 minutes with tadalafil, and 15 minutes with avanafil. However, success rates after 20 minutes are much less than after 1 hour for sildenafil, vardenafil, and tadalafil; therefore, if patients do not experience a rapid beneficial effect, they should be advised to delay sexual intercourse for one (sildenafil or vardenafil) or 2 hours (tadalafil)—when serum concentrations have peaked. High-fat meal intake has been shown to delay absorption of avanafil, vardenafil, and sildenafil; this effect is not seen with tadalafil (Carson and Lue, 2005).

4. Period of efficacy—Tadalafil therapy has a broader window of clinical responsiveness than avanafil, sildenafil, or vardenafil because of its longer half-life (17.5 vs 4–5 hours for sildenafil or vardenafil). Tadalafil enhances erectile function in men with ED for up to 36 hours and may mean less planning and pressure to have sexual intercourse according to a schedule. For avanafil, duration of efficacy is 4–6 hours, similar to those for sildenafil and vardenafil.

5. Adverse events—In randomized controlled trials, flushing (10%) and visual side effects were more common in patients receiving sildenafil or vardenafil, and back pain/myalgia (1–4%) was more common for tadalafil users. These events were mostly mild, abated with time (within 2–4 weeks), and prompted treatment discontinuation in only a small number of patients (Brock et al, 2002; Porst et al, 2003; Goldstein et al, 1998). Except for visual disturbances, the other reported side effects of PDE5Is (headaches 15%, flushing, rhinitis 5–10% for vardenafil and sildenafil, slight lowering of blood pressure, dyspepsia, etc) are likely caused by PDE5 inhibition in vascular or gastrointestinal smooth muscle.

6. Warnings and drug interactions—ED is common among men who have atherosclerotic coronary artery disease. With respect to overall cardiac safety, controlled and postmarketing studies of the four FDA-approved PDE5Is demonstrated no increase in MI or death rates in double-blinded, placebo-controlled, or open-label studies when compared with expected study population rates. Patients who have an acute MI after a PDE5I may be given standard therapies except for organic nitrates. Nitroglycerin should not be given with 24 hours of sildenafil or vardenafil use, 48 hours for tadalafil, and 12 hours for avanafil. At present, there is no pharmacologic antidote to the PDE5 inhibitor–nitrate interaction (Kostis et al, 2005). Caution is also advised when an α-blocker and a PDE5 inhibitor are given together, as they induce an interaction that can lead to excessive vasodilation and hypotension.

Because of its effect on QTc interval, vardenafil is not recommended for patients who take type 1A antiarrhythmics (such as quinidine or procainamide) or type 3 antiarrhythmics (such as sotalol or amiodarone), or for patients with congenital prolonged QT syndrome.

There have been cases of sudden hearing loss, both with and without accompanying vestibular symptoms (tinnitus, vertigo, or dizziness), reported in patients using PDE5Is, which prompted the FDA to request drug labeling changes in 2007. Although no causal relationship has been demonstrated, the FDA believed that the strong temporal relationship between the use of PDE5 inhibitors and sudden hearing loss in these cases warranted revisions to the product labeling for the drug class.

Finally, there have been reports of the development of nonarteritic anterior ischemic optic neuropathy (NAION) in men using PDE5Is. Epidemiologically, NAION is the second most common acquired optic neuropathy in men aged 50 years and older. Risk factors for NAION, cardiovascular disease, and ED are shared and include age, dyslipidemia, diabetes, hypertension, and cigarette smoking. Given the large number of men safely using these agents and a limited number of events, it is not possible to determine whether NAION is directly linked to the use of PDE5Is. Nevertheless, physicians should continue to advise patients to discontinue the use of a PDE5 inhibitor and seek immediate medical attention in the event of a sudden loss of vision as a safety measure (Sikka et al, 2013).

7. Contraindications—PDE5Is are contraindicated for patients using nitrates, as a precipitous and potentially life-threatening hypotensive episode may occur with concurrent use. PDE5Is are either not recommended or are to be used with caution in men with unstable angina, cardiac failure, recent MI, uncontrolled or life-threatening arrhythmia, or poorly controlled blood pressure (resting BP <90/50 mm Hg or >170/100–110 mm Hg).

8. Starting doses—The recommended starting doses are 50 mg for sildenafil, 10 mg for vardenafil and tadalafil, and 50 mg for avanafil. The dose may be increased to 100 mg (sildenafil) or 20 mg (vardenafil or tadalafil) or decreased to 25 mg or 5 mg, respectively, based on individual efficacy and tolerability. Starting dosage for avanafil is 50 mg with the option to increase to 100–200 mg as needed. Several reports have shown that a daily dose of 5 mg of tadalafil reduced side effects while matching the effectiveness of 20 mg of tadalafil taken as needed (Seftel et al, 2009). Patients should also be counseled to trial a PDE5I several times before declaring it "ineffective"; for instance, the cumulative probability of success with sildenafil increases with the first 9–10 attempts, after which it stabilizes (McCullough et al, 2002).

B. Centrally Acting Oral Agents

Apomorphine is a proerectile D_1/D_2 dopamine receptor agonist, but it may also stimulate 5-HT(2C) receptor to enhance penile erection (Kimura et al, 2008). Uprima, a sublingual form designed for buccal absorption, has been approved for ED in Europe (but not in the United States) and reported to induce erection in 67% of men with psychogenic ED. Apomorphine has a rapid onset of action, with a window of sexual opportunity of approximately 2 hours from ingestion. Maximal plasma concentrations are reached in 50 minutes. In a double-blinded placebo-controlled study of 2- and 4-mg dosages, erections firm enough for intercourse were reported by 45% and 55% of patients, respectively, with placebo responses of 35% and 36%. Adverse events included nausea 16.9%, dizziness 8.3%, sweating 5%, somnolence 5.8%, yawning 7.9%, and emesis 3.7%. There were no documented food–drug interactions in clinical trials (with the exception of ethanol) and specifically, no documented pharmacologic interactions for subjects using nitrate drugs.

Yohimbine is a centrally acting α_2-adrenergic antagonist that is not recommended for use in the treatment of ED by the 2005 American Urological Association guidelines (reviewed and validity confirmed in 2011) (Montague et al, 2005). Side effects include gastrointestinal intolerance, palpitations, headache, agitation, anxiety, and increased blood pressure (precautions are advised in men with cardiovascular disease). Trazodone is also not recommended; efficacy in pooled analyses was statistically equivalent to placebo. Side effects include drowsiness, nausea, emesis, blood pressure changes (both hypotension and hypertension are reported), urinary retention, and priapism (especially at therapeutic antidepressant levels) (Montague et al, 2005).

▶ Transurethral Therapy

Alprostadil, a synthetic formulation of prostaglandin E1, is the only FDA-approved pharmacologic agent approved for the management of ED via intracavernous and transurethral routes. After absorption from the urethra to the corpus spongiosum and then corpus cavernosum, alprostadil stimulates adenyl cyclase to increase intracellular levels of cAMP and lower levels of intracellular calcium, thereby relaxing arterial and trabecular smooth muscle. **Medicated urethral system for erection (MUSE)** treatment consists in administration of a small semisolid pellet (3 × 1 mm) into the distal urethra (2–3 cm) by a proprietary applicator (MUSE, VIVUS Inc, Menlo Park, CA, USA). Clinical studies showed that 66% of men responded to in-office trials; however, postmarketing studies have produced less successful results of about 50% (Mulhall et al, 2001). Penile rigidity can be enhanced by placing an elastic ring at the base of the penis to mechanically assist veno-occlusion. Penile and/or scrotal pain or discomfort is a ubiquitous side effect of alprostadil-based therapies and is clearly dosage-related and was reported in 33% of men in MUSE trials. Hypotension and syncope have been noted in 1–5.8% of patients, thus mandating initial trial dose administration in the office setting. Some female partners also report vaginal discomfort (about 10%) after ejaculation by a man using MUSE.

▶ Intracavernous Injection

Intracavernous injection (ICI) of vasoactive drugs is considered the most effective nonsurgical therapy for ED. It remains the first-line therapy for select patients and a valuable treatment option for PDE5I nonresponders or those who cannot tolerate side effects of oral agents. ICI treatment offers several potential advantages to the patient, including a rapid onset of action, essentially no systemic side effects and drug interactions, and dependable efficacy for all forms of ED. Men who have failed first-line oral pharmacotherapy constitute the largest group of ICI-treated patients, with a significant erectile response rate of >80% demonstrated among PDE5I nonresponders, indicating that progression to second-line injection therapy is appropriate. A list of drugs that have been used clinically is presented in Table 39–5, and the most commonly used agents and combinations are discussed below.

A. Papaverine

Papaverine, an alkaloid isolated from the opium poppy, induces relaxation of cavernous smooth muscle and penile vessels via nonspecific inhibition of phosphodiesterase. It is metabolized by the liver, with a plasma half-life of 1–2 hours. Monotherapy doses range from 15 to 60 mg. Advantages include low cost and stability at room temperature, while adverse effects include priapism (up to 6%), corporal fibrosis (6–30%; assumed to be associated with poor technique, minimal injection site compression time, >1 mL injection volume, pH 3–4), and occasional elevation of liver enzymes (Bella and Brock, 2004).

Table 39–5. Intracavernous vasodilator injection therapy.[a]

Drug	Test dose	Therapeutic dose
Papaverine	15–30 mg	15–60 mg
Alprostadil	5–10 μg	5–60 μg
Papaverine (30 mg) + phentolamine (1 mg)	0.1–0.3 mL	0.1–1 mL
Papaverine (30 mg) + phentolamine (1 mg) + alprostadil (10 μg)	0.1–0.3 mL	0.1–1 mL

[a] Lower doses are recommended for management of neurogenic and psychogenic impotence.

B. Alprostadil (Prostaglandin E1)

Alprostadil causes smooth-muscle relaxation, vasodilation, and inhibition of platelet aggregation through elevation of intracellular cAMP. It is metabolized by the enzyme prostaglandin 15-hydroxydehydrogenase, which has been shown to be active in human corpus cavernosum. After ICI, 96% of alprostadil is locally metabolized within 60 minutes, and no change in peripheral blood levels is observed. Alprostadil has been approved by the FDA for intracavernous therapy as Caverject (Pfizer, NYC) and Edex (Schwarz Pharma, Milwaukee, WI). Cumulative data yield a success rate of 70–75% across ED etiologies, utilizing a median dose of 12–15 μg. Common adverse effects include pain at the injection site or during erection (11–15%), small hematoma or bruising, penile fibrosis (1–3%), and a burning sensation at time of injection. Rates of priapism are low (1–3%), and systemic side effects are rare (Bella and Brock, 2004).

C. Drug Combinations

The most commonly used drug combinations for ICI in the United States are bimix (papaverine/phentolamine) and trimix (papaverine/phentolamine/alprostadil) in various concentrations (Montorsi et al, 2010). A combination of vasoactive intestinal polypeptide and phentolamine has also been used in other countries. Multiple series have demonstrated patient satisfaction rates of >75% and low rates of priapism or fibrosis. Side effects are reduced, as smaller amounts of each agent are required, and the targeting of multiple pathways increases therapeutic efficacy.

D. Adverse Effects

Priapism (discussed exclusively in the penultimate section of this chapter) and fibrosis are the two serious side effects associated with ICI therapy. Priapism occurred in 1.3% of 8090 patients in 48 studies with alprostadil, which is about 5 times lower than the percentage obtained with papaverine or bimix (1.5% vs 10% vs 7%) (Linet and Ogrime, 1996). Fibrosis can occur as a nodule, diffuse scarring, plaque, or curvature. Scar tissue can be prevented by >5 minutes of compression of the injection site to reduce bleeding and trauma. Priapism is best prevented by careful dosage titration.

E. Dosage and Administration

Patients must have the first injection performed by medical personnel and receive appropriate training and education before home injection. An initial dose of 2.5 μg for alprostadil is recommended. If the response is inadequate, increases in 2.5-μg increments can be given until a full erection is achieved or a maximum of 60 μg is reached. For drug combinations, treatment is initiated with a small dose (eg, 0.1 mL) and titrated according to erectile response. The goal is to achieve a full erection of <1-hour duration to avoid priapism.

F. Treatment of Prolonged Erection or Priapism

The best treatment is prevention. Prolonged erections, a potentially devastating adverse effect of ICI, are often secondary to rapid dose escalation by the patient, missed initial injection with second attempt, or use among neurogenic and/or young patients. It is imperative that the clinician prescribing intracavernous therapies emphasize to the patient that priapism represents a urologic emergency and that any erection lasting > 4 hours necessitates urgent medical evaluation. The best regimen for averting priapism is ICI of diluted phenylephrine 250–500 μg every 3–5 minutes until detumescence. In patients with cardiovascular disease, monitoring of blood pressure and pulse is recommended (Montague et al, 2003). If the priapism lasts for more than 2–3 days, cavernosum–glans shunt with intracavernous tunneling may be required (Inman et al, 2009).

G. Contraindications

Intracavernous injection is contraindicated in patients with sickle cell anemia, schizophrenia, or another severe psychiatric disorder. Because monoamine oxidase (MAO) is involved in catecholamine (including phenylephrine) metabolism, if a man on a MAO inhibitor were to develop prolonged erection/priapism after ICI, a simple cavernosum–glans shunt might constitute a better treatment than intracavernous injection of phenylephrine. For patients using an anticoagulant or aspirin, compressing the injection site for 7–10 minutes after injection is recommended. In patients with poor manual dexterity, the sexual partner can be instructed to perform the injection.

▶ Vacuum Constriction Device

The vacuum constriction device consists of a plastic cylinder connected directly or by tubing to a vacuum-generating source (manual or battery-operated pump). Only devices containing a vacuum limiter should be used, as injury to the penis may occur with extremely high negative pressures (Montague et al, 2005). After the penis is engorged, a constricting ring is applied to the base to maintain the erection. The ring may be uncomfortable or painful; to avoid injury, it should not be left in place for less than 30 minutes. The erection produced differs from a physiologic or ICI-induced erection as the portion of the penis proximal to the ring is not rigid, which may result in a pivoting effect. The penile skin may be cold and dusky, and ejaculation may be trapped by the constricting ring. Complications include penile pain and numbness, difficult ejaculation, ecchymosis, and petechiae. Patients taking aspirin or Coumadin (warfarin) should exercise caution when using these devices.

In some patients, the device can produce an erection that is of sufficient rigidity for coitus or engorge the glans for men with glanular insufficiency. In patients with severe vascular insufficiency, the device may not produce adequate erection. Although it is a safe and less costly means of treating ED when used properly, low patient acceptability limits the application or use of this therapy.

▶ Follow-up Strategy

Regardless of the treatment regimen chosen, follow-up is essential to ensure optimal outcomes. Modification of lifestyle, diet change, regular exercise, and smoking abstinence or cessation should be reassessed and encouraged at each clinic visit. Monitoring adverse events, assessing satisfaction or failure with a given treatment, identifying a partner's sexual dysfunction, and assessing overall health and psychosocial function are key considerations. In patients who do not respond to first-line therapy (oral PDE5 inhibitor therapy), an alteration in dose or treatment might be of value, as most second- and third-line options have demonstrated reasonable response and satisfaction rates in controlled studies (Lue et al, 2004).

PENILE VASCULAR SURGERY

Isolated stenosis or occlusion of extrapenile arteries may be amenable to surgical repair. Arterial reconstructive surgery is a treatment option for healthy men, usually aged 55 or younger, with acquired ED secondary to focal arterial occlusion and the absence of severe veno-occlusive disorder or generalized vascular disease secondary to hyperlipidemia, diabetes mellitus, chronic hypertension (Montague et al, 2005). The most commonly used technique for penile revascularization is placement of a bypass from the inferior epigastric artery to the dorsal artery or deep dorsal vein of the penis.

Penile venous surgery is also indicated only in young men with congenital or traumatic venous leakage. In congenital venous leakage, the venous insufficiency is typically through abnormal crural veins or superficial dorsal vein and is amendable to surgical cure. Traumatic venous leak is usually due to localized damage to the tunica albuginea or formation of a "fistula" between the corpus cavernosum and corpus spongiosum. Repair of the tunica or closure of the fistula can result in significant improvement of erectile function. In older men with chronic systemic diseases, venous leakage is usually caused by atrophy of the cavernous smooth muscle and degeneration of tunica albuginea; ligation of penile vein will only produce transient improvement and is not recommended.

PENILE PROSTHESIS

Patients considered for prosthesis implantation should be made aware of types of prosthesis available, efficacy, and potential complications, including infection, mechanical failures, cylinder or tubing leaks, perforation, persistent pain, penile shortening, and autoinflation. Penile prostheses are divided into three general types: malleable (semirigid), mechanical, and inflatable devices. The malleable devices are made of silicone rubber, and several models contain a central intertwined metallic core. The mechanical device is also made of silicone rubber but contains polytetrafluoroethylene-coated interlocking polysulfone rings in a rod column, which provides rigidity when the rings are aligned in a straight line and flaccidity when the penis is bent. Inflatable (hydraulic) devices are further divided into two- and three-piece devices. Two-piece inflatable prostheses consist of a pair of cylinders attached to a scrotal pump reservoir. The most commonly used device, the three-piece inflatable penile prostheses, consists of paired penile cylinders, a scrotal pump, and a retropubic fluid reservoir (Table 39–6).

In general, the malleable devices last longer than the inflatable ones. Modern three-piece prostheses are extremely durable and reliable. However, patients should be informed that a 5–15% failure rate is expected within the first 5 years for inflatable implants, and most devices will fail in 10–15 years and need replacement. Patient satisfaction with the three-piece device is high, exceeding 85–90% in appropriately selected patients. Recent innovations in penile prosthetics include antibiotic and hydrophilic-coated devices (infection rate <1%), lockout valves to prevent autoinflation, and a

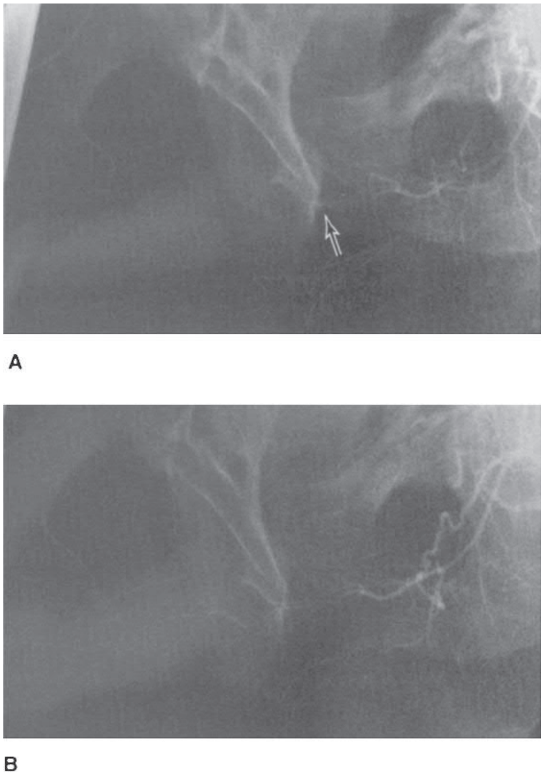
Table 39–6. Types of penile prostheses.

Semirigid
American Medical System (AMS) Spectra
Coloplast Genesis
Two-piece inflatable
AMS Ambicor
Three-piece inflatable
Coloplast Titan with standard and narrow-base cylinder
AMS 700 MS series: CX, CXR, LGX

more patient-friendly pump (Knoll et al, 2009; Wolter and Hellstrom, 2004).

PHYSIOLOGY OF EMISSION, EJACULATION, AND ORGASM

Different mechanisms are involved in erection, emission, ejaculation, and orgasm, and these events can be dissociated from one another (eg, a frequent complaint of men with ED is ejaculating through a "limp penis"; see Figure 39–6). Except for nocturnal emissions, or "wet dreams," emission and ejaculation require stimulation of the external genitalia. Impulses traveling from the pudendal nerves reach the upper lumbar spinal sympathetic nuclei. Efferent signals traveling in the hypogastric nerve activate secretions and transport sperm from the distal epididymis, vasa deferentia, seminal vesicles, and prostate to the prostatic urethra. Coordinated closing of the internal urethral sphincter and relaxation of the external sphincter direct the semen into the bulbous urethra (emission). Subsequent rhythmic contractions of the bulbocavernous muscles force the semen through a pressurized conduit—the constricted urethral lumen compressed by the engorged corpus spogiosum—to produce the 2–5-mL ejaculate. The external ejaculation process involves the somatomotor efferent of the pudendal nerve to contract the bulbocavernous muscle. Since this action is involuntary, however, integrated autonomic and somatic action is required.



▲ **Figure 39–6.** Internal iliac arteriogram in the flaccid penis *(**A**)* shows poor visualization of penile arteries, simulating occlusion (*arrow*). After intracavernous injection of 60 mg of papaverine *(**B**)*, all the branches of the penile artery are well visualized.

The mechanism of orgasm is the least understood of the sexual processes. It probably involves cerebral interpretation and response to sexual stimulation. Along with emission and ejaculation, several nongenital responses also occur. These include involuntary rhythmic contractions of the anal sphincter, hyperventilation, tachycardia, and elevation of blood pressure.

▶ Disorders Affecting Ejaculation, Emission, and Orgasm

Premature or rapid ejaculation (PE), a persistent or recurrent occurrence of ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it, is reported by up to 20–30% of men (Althof, 2006). Some propose that the definition of premature ejaculation should include rapidity of ejaculation, lack of control, and negative consequences (McMahon et al, 2004). In addition to psychotherapy or behavioral therapy, current guidelines suggest an SSRI, such as paroxetine (10–40 mg daily or 20 mg 3–4 hours before intercourse) may be used as pharmacotherapy for PE, although this indication is not FDA-approved (Montague et al, 2004). Penile sensitivity may be reduced with use of a condom or topical anesthetizing cream (lidocaine–prilocaine). Although time to ejaculation is prolonged, a significant percentage of men experience decreased pleasure (penile numbness) or loss of erection. A short-acting SSRI, dapoxetine hydrochloride, has been developed for on-demand use in PE but has not been approved by the FDA. Its pharmacokinetic profile is characterized by rapid absorption, a short initial half-life of 1.3–1.4 hours, and rapid elimination with minimal accumulation even after multiple dosing. Several large phase III studies have demonstrated that dapoxetine can increase intravaginal ejaculatory latency time and improve several patient-reported outcomes relevant to control of ejaculation and satisfaction with intercourse. The most common adverse events were nausea, dizziness, diarrhea, and headache. There were no signals for treatment-emergent anxiety or SSRI discontinuation syndrome after abrupt withdrawal (Owen, 2009).

A history of disease or surgery is helpful in differentiating emission failure from **retrograde ejaculation**. If microscopic examination confirms the presence of sperm in bladder urine after a dry ejaculation, retrograde ejaculation can be diagnosed. If no sperm is found, emission failure is the cause. Bilateral sympathectomy at the L2 level may result in ejaculatory dysfunction in about 40% of patients, while high bilateral retroperitoneal lymphadenectomy causes an even higher percentage of emission failures. Retrograde ejaculation is usually the result of dysfunction of the internal sphincter or the bladder neck, as seen after prostatectomy, with α-blocker therapy, and in autonomic neuropathy due to diabetes.

Elimination of α-adrenergic blockers may cure some patients with emission failure or retrograde ejaculation. α-Sympathomimetics, such as ephedrine or a combination of chlorpheniramine maleate and phenylpropanolamine hydrochloride, have been used successfully in patients with retrograde ejaculation (McMahon et al, 2004). Electroejaculation via a rectal probe has been applied in patients suffering from spinal cord injury with some success (Soeterik et al, 2016). Psychosexual counseling is appropriate for patients who have normal wet dreams but cannot achieve orgasm and ejaculation.

Viberect is a handheld device (Reflexonic, LLC, Chambersburg, PA, USA) FDA-cleared for treatment of ED. It may also be employed for men with delayed ejaculation/orgasm or decreased penile sensation. It exploits vibratory stimulation of genital afferent nerves for provoking erections via neurostimulatory principles. One study of the device involved treatment of five young men (mean age 26 years, with normal erectile function) at 75 Hz with ventral stimulation without any external visual sexual stimulation. Both objective Rigiscan measurements of rigidity and subjective Erection Hardness Score (EHS) responses were recorded and correlated. Treatment yielded scores of EHS 4/4 (penis is completely hard and fully rigid) in two subjects, 3/4 (penis hard enough for penetration but not completely hard) in two other subjects, and 2/4 (penis is hard but not enough for penetration) in one subject. There were no complications, and all subjects felt that Viberect would be a reasonable, practical ED treatment (Segal et al, 2013). Viberect may be particularly useful for patients who complain of delayed orgasm and decreased penile sensation and for spinal cord injury patients to promote ejaculation. Successful emission and ejaculation without orgasm does occur in some patients with spinal cord injury.

PEYRONIE'S DISEASE

Peyronie's disease (PD), or plastic induration of the penis, is an acquired, progressive connective-tissue disorder of the tunica albuginea of the penis. This may lead to penile pain, penile curvature or deformity, difficulty or inability to have penetrative intercourse, and palpable plaque on physical examination. Frequently, PD dramatically affects quality of life, having adverse effects on relationships, and resulting in significant physical and psychological distress in both the patients and their sexual partners (Smith et al, 2008).

Epidemiology of Peyronie's Disease

The prevalence of PD is estimated to be between 3 (Schwarzer et al, 2001) and 9% of the male population (Mulhall et al, 2004), but true prevalence may be even higher. PD patients are usually between the ages of 45 and 60 years (Mulhall et al, 2004); however, 10% of patients are younger than 40 years, including teenagers (Tefekli et al, 2001; Tal et al, 2012). PD is more common in Caucasian men (Tal et al, 2010).

It is estimated that PD occurs in 8% of diabetes mellitus (type 2) patients (El-Sakka and Tayeb, 2005), 16% of radical prostatectomy patients (Tal et al, 2010), and 20% of patients with both diabetes and ED (Arafa et al, 2007). A family history of PD is found in only 2% of patients (Bella et al, 2007). Up to 21% of patients with Dupuytren's contractures (DC) also have PD (Carrieri et al, 1998). Studies show similar patterns of gene expression in families with both PD and DC, specifically in regard to collagen degradation, ossification, and myofibroblast differentiation (Qian et al, 2004).

Anxiety, depression, low self-esteem, and relationship disorders are reported by more than half of PD patients (Smith et al, 2008; Nelson et al, 2008; Gelbard et al, 1990). Interestingly, the degree of distress does not necessarily correlate with the degree of penile curvature or deformity (Rosen et al, 2008). ED is a common association in 20–50% of men with PD. ED is most often multifactorial, occurring as a result of penile pain during erection, functional disability as a result of the curvature or vascular disease causing flail penis, and psychogenic due to performance anxiety and fear of partner rejection (Gelbard et al, 1990).

Pathogenesis of Peyronie's Disease

The underlying pathogenesis of PD is unknown, but the process is likely related to aberrant wound healing, genetic predisposition, repetitive microtrauma to the erect penis during intercourse, and subsequent tissue ischemia.

Natural History of Peyronie's Disease

Peyronie's disease is an acquired, progressive two-phase connective-tissue disease of the tunica albuginea. The **acute** (inflammatory or active) **phase** of PD is characterized by penile inflammation associated with penile pain in the flaccid or erect state, growth of penile plaque, and progressive deformity. Pain is present in 35–45% of patients during the early stages of the disease and usually resolves in 90% of patients during the first 6 months (Hatzimouraditis et al, 2012). When the inflammation resolves and the pain, plaque, and penile deformity stabilize, the disease has evolved to the **chronic** (fibrotic or stable) **phase,** usually occurring 6–12 months after onset. At this stage, improvements in penile curvature and deformity are rare (Mulhall et al, 2006). Although urologists address PD as a two-phase disease process, the natural history of PD can vary. Studies show that without treatment penile deformity worsens in 30–50% of patients, stabilizes in 47–67%, and improves in 3–13% of patients (Gelbard et al, 1990; Mulhall et al, 2006; Kadioglu et al, 2002).

Assessment and Diagnosis

The diagnosis of PD is apparent from patient history and physical examination. A full sexual history should be taken, and physical examination should include the hands and feet for detection of possible Dupuytren's contracture of the palms or Ledderhose scarring of the plantar fascia (Mulhall et al, 2006), which are commonly associated with PD (Hatzimouratidis et al, 2012).

Genitourinary examination will typically reveal well-defined, palpable tunical plaques in classical PD. Objective assessments may include stretched penile length, measurement of plaque size, and assessment of erectile function and penile curvature/deformity during erection using either patient-produced photography of a natural erection, after use of a vacuum erection device, or after intracavernosal injection of a vasoactive agent in clinic (Hatzimouratidis et al, 2012). Additional data may be obtained from imaging studies, with ultrasound having the highest sensitivity for plaques in the tunica albuginea compared to other imaging modalities. Ultrasonography provides information about both the calcified and the soft-tissue elements of PD plaques as well assessment of penile vascular status if Doppler duplex ultrasound is performed during erection.

Medical Treatment of Peyronie's Disease

Determining the appropriate treatment depends on a variety of factors: the stage of the disease, the presence of pain, severity and direction of the curvature, penile length, and patient's erectile status (Garaffa et al, 2013). Nonsurgical treatment of PD aims to alleviate penile pain, to halt disease progression, and to stabilize inflammation, plaque development, and penile deformity (Gur et al, 2011). Nonsurgical treatments include oral pharmacotherapies, topical treatments, and intralesional injection therapy.

Oral therapy is indicated in men with acute disease and penile deformity associated with bother. We suggest pentoxifylline as first-line oral therapy to be used as a key component of multimodal therapy that also includes intralesional injection (Alwaal et al, 2015) and traction (Usta and Ipekci, 2016) at the appropriate time during disease progression. Pentoxifylline is a nonspecific phosphodiesterase inhibitor that inhibits TGFβ1-mediated inflammation, prevents deposition of collagen type 1, and increases nitric oxide. Various other options for oral therapy have been suggested, including colchicine, PDE5Is, vitamin E, potaba, tamoxifen, carnitine, coenzyme Q10, and omega-3 fatty acids. While preliminary outcomes for most of these therapies were promising, well-designed randomized placebo-controlled trials have been disappointing and fail to demonstrate much benefit (Hatzimouratidis et al, 2012).

Intralesional therapy allows for direct injection of a pharmacological agent into the penile plaque, thus avoiding systemic side effects and ensuring high concentrations of the agent inside the plaque. These therapies are generally safe and well tolerated. There are three intralesional drug treatments that have shown efficacy in randomized trials: collagenase, verapamil, and interferon-α-2b. Collagenase clostridium histolyticum is the only FDA-approved intralesional treatment for men with Peyronie's disease and has been enthusiastically adopted as the intralesional treatment of choice. The medication is restricted under a **risk evaluation and mitigation strategy (REMS)**. Treatment course consists of several cycles per plaque, and each cycle consists of two injections separated by 1–3 days to allow for penile swelling and discomfort to resolve between injections, making the subsequent injection easier. Penile modeling procedures are an essential component of the treatment and should begin 48 hours after the second injection or sooner if tolerated. The interval between cycles should be no shorter than 6 weeks (Tan et al, 2014). Adverse effects include penile pain, contusions, ecchymosis, swelling, redness and itching at or around the injection site, and major severe adverse events including penile ruptures requiring surgical repair in the clinical trials.

Other medical modalities, such as iontophoresis, topical therapies, extracorporeal shockwave therapy, and radiation therapy, are not recommended (Chung et al, 2016).

Surgical Treatment of Peyronie's Disease

When nonsurgical treatment fails to correct the deformity, surgical treatment can be considered. Published, evidence-based guidelines recognize certain patient disease characteristics as indications for surgery: deformity that impairs sexual function, stabilized disease, extensive plaque calcification, failed minimally invasive treatment, and desire for rapid and reliable results (Hatzimouratidis et al, 2012; Chung et al, 2016; Nehra et al, 2015). The goals of surgery are to correct the deformity, to maintain satisfactory penile length and girth, and to preserve rigidity to allow for restoration of penetrative intercourse (Garaffa et al, 2013). Surgery is ideally performed after the disease has been stable for at least 3–12 months (Chung et al, 2016; Nehra et al, 2015; Kendirci and Hellstrom, 2004).

Surgical risks include de novo or worsened ED, penile shortening, temporary or permanent penile hypoesthesia, chronic pain, the potential for palpation of permanent suture below the skin, and poor cosmesis of the surgical scar (Montorsi et al, 2010). Recurrent curvature may also develop because surgery was performed prematurely prior to stabilization, reactivation of the condition, or the use of absorbable sutures.

Procedures for correction of deformities caused by PD are classified as either penile shortening procedures performed on the convex (longer) side of the penis or penile lengthening procedures performed on the concave (shorter) side of the penis. Lengthening procedures are used to avoid penile shortening or to correct complex deformities, including hourglass or indent deformities, and require the use of a graft, which carries a higher risk of erectile dysfunction and penile hypoesthesia. Penile prosthesis should be considered in PD associated with ED refractory to medical treatments (Nehra et al, 2015). The choice of the surgical technique employed for PD depends on various factors, including penile length, location and degree of curvature, erectile function, patient goals, and patient and surgeon preference.

PRIAPISM

Priapism, one of the most common urologic emergencies, is defined as a prolonged and persistent penile erection that is unrelated to sexual interest or stimulation and lasts longer than 4 hours (Montague et al, 2003). Three types of priapism have been described: ischemic (low flow), nonischemic (high flow), and stuttering (recurrent).

Epidemiology and Pathogenesis

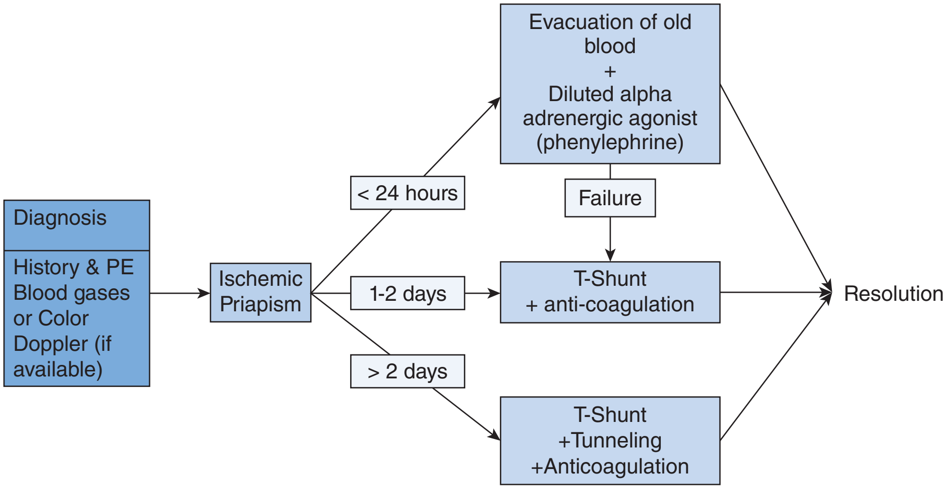
Ischemic priapism, the most common presentation of priapism, has an incidence of up to 5.34 per 100,000 men per year. It is most often idiopathic, and it disproportionately affects sickle cell disease patients (Roghmann et al, 2013). Ischemic priapism results from occlusion of the venous outflow of the corpora cavernosa; this prevents arterial inflow and leads to a cascade of tissue ischemia, endothelial and smooth-muscle damage, and eventual fibrosis (Montague et al, 2003; Spycher and Hauri, 1986). Although most often idiopathic, known etiologies of ischemic priapism include malignancy, medications, spinal cord injury, sickle cell disease, and glucose-6-phosphate deficiency (Broderick et al, 2010).

Occurring less frequently, **nonischemic priapism** is usually the result of trauma to the perineum or penis (Shigehara and Namiki, 2016). This condition is not a medical emergency. After penile trauma to the penis, vascular injury to the cavernosal artery or helicine arteries is exacerbated by erection (Mwamukonda et al, 2010; Wu and Lue, 2010). When a fistula forms between the artery and the sinusoidal spaces of the corpora, the subsequent unregulated arterial inflow results in persistent, painless penile tumescence. As venous drainage is preserved, the penile tissue does not become ischemic, and the condition is generally painless (Brock et al, 1993).

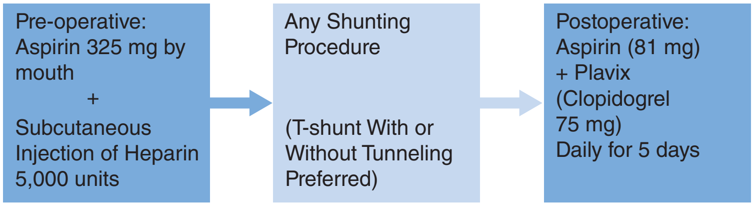
Recurrent ischemic, or **stuttering**, **priapism** is defined as periodic episodes of prolonged erections that may lead to recurrent ischemic priapism. The underlying molecular mechanisms of ischemic priapism are under continued investigation. Because stuttering priapism affects sickle cell disease patients more commonly than others, microvascular occlusion secondary to hemolysis with stasis of sickled erythrocytes is thought to be a significant contributing factor (Adeyoju et al, 2002). Animal models and clinical studies have also revealed a role for improper PDE5 regulation and abnormal nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) signaling and regulation in the pathogenesis of stuttering priapism (Champion et al, 2005; Lagoda et al, 2014; Anele and Burnett, 2015).

Treatment of Priapism

For **ischemic priapism** (Figure 39–7), prompt treatment is essential to ensure the least amount of long-term disability, that is, penile fibrosis and persistent erectile dysfunction. Treatment can be initiated with corporal aspiration through a 21-gauge butterfly needle with subsequent injection of a diluted α-adrenergic



▲ **Figure 39–7.** Management of ischemic priapism. (Reproduced with permission from Hudnall M, Reed-Maldonado AB, Lue TF: Advances in the understanding of priapism, Transl Androl Urol. 2017 Apr;6(2):199–206.)


Pre-operative:
Aspirin 325 mg by mouth
+
Subcutaneous Injection of Heparin 5,000 units
Any Shunting Procedure
(T-shunt With or Without Tunneling Preferred)
Postoperative:
Aspirin (81 mg)
+ Plavix (Clopidogrel 75 mg)
Daily for 5 days

▲ **Figure 39–8.** Perioperative anticoagulation to prevent recurrence of priapism. (Reproduced with permission from Hudnall M, Reed-Maldonado AB, Lue TF: Advances in the understanding of priapism, Transl Androl Urol. 2017 Apr;6(2):199–206.)

agent, such as phenylephrine (500 µg delivered every 5 minutes), the preferred agent for early management (Montague et al, 2001). Other vasoactive agents, such as oral terbutaline, have been deemed less effective than phenylephrine (Martin and Cocchio, 2016). If this is ineffective, or if the duration of the episode has been prolonged (for >24–48 hours), a shunt procedure may be performed. Typically, a distal shunt between the corpora and the glans is created using a percutaneous (Ebbehoj or Winter shunt, T-shunt) or open (Al-Ghorab) procedure (Kovak et al, 2013; Segal et al, 2013; Garcia et al, 2008). The choice often depends on surgeon familiarity but should proceed from least to most invasive. In the past, proximal shunts (Quackels, 1964) and cavernosum-venous shunts (Barry, 1976) were the standard approaches. However, these technically challenging, lengthy procedures have been replaced by tunneling procedures developed by Lue and colleagues (Garcia et al, 2008; Brant et al, 2009) and Burnett and colleagues (Segal et al, 2013; Burnett and Pierorazio, 2009).

One of the most frequent complications of shunting procedures for ischemic priapism is shunt failure. All shunts require incision through the tunica albuginea, exposing collagen to coagulation factors in the blood, and consequently activating the clotting cascade and causing premature shunt closure in some cases. Perioperative anticoagulation (heparin 5000 units SQ and aspirin 325 mg PO) should be initiated immediately after identifying the need for a surgical shunt procedure and continued into the postoperative period for at least 5 days (aspirin 325 mg PO per day + clopidogrel 75 mg PO per day). Appropriate anticoagulation will minimize shunt failure (Lue and Garcia, 2013) (Figure 39–8).

For patients with ischemia lasting longer than 48 hours, early implantation of a penile prosthesis has been suggested. Implantation within 4 weeks of the ischemic episode may result in fewer postoperative complications, such as erosion or infection, than implantation delayed for several months, with patients reporting higher satisfaction and less penile shortening with early implantation (Zackarakis et al, 2014). Immediate implantation of a malleable penile prosthesis is an option that allows for future upsizing with an inflatable prosthesis without significant difficulty at a later operation and may lead to long-term cost savings and decreased utilization of hospital resources (Zackarakis et al, 2015). Early implantation of a penile prosthesis is not obligatory.

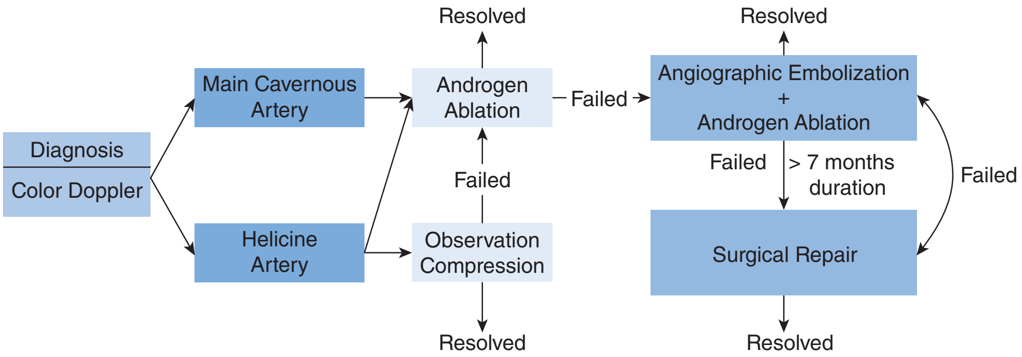
For **nonischemic priapism**, treatment options include observation, medical management, selective arterial embolization, and surgical intervention as the last resort (Montague et al, 2003). Observation and penile compression represent the typical initial treatment option as the condition may resolve spontaneously. Medical therapy with androgen ablation for 1–3 months can provide an effective option for nonischemic priapism that is caused by damage to the cavernous artery (Mwamukonda et al, 2010; Wu and Lue, 2012). Androgen blockade is assumed to reduce sleep-related erections and facilitate closure of the vascular injury after trauma. With transient side effects and minimal attendant morbidity, medical therapy circumvents the need for invasive interventions (Mwamukonda et al, 2010) (Figure 39-9).

If medical therapy fails, selective arterial embolization with autologous clot, gel foam, or coiling is an option (Hakim et al, 1996). Computed tomographic angiography can be used to identify the damaged vessel (Tan et al, 2015).

Finally, in patients who present with **stuttering priapism**, androgen ablation therapy is an effective, proven therapy for eliminating the erection-promoting effects of androgens (Salonia et al, 2014). In men with sickle cell disease, treatment with continuous, low-dose daily type 5 phosphodiesterase inhibitors may normalize otherwise dysregulated PDE5 levels and decrease the frequency of priapism episodes (Burnett et al, 2006, 2014). As scientists discover more about the pathophysiology and mechanisms of recurrent ischemic priapism, additional opportunities for pharmacologic intervention and management will become available. The primary goal of contemporary management of stuttering priapism is to prevent additional episodes to reduce the risk of progression to a major ischemic event (Anele et al, 2015).

THE FUTURE OF ERECTILE DYSFUNCTION TREATMENT

With the exceptions of lifestyle modifications and revascularization procedures, current interventions for ED merely treat ED, offering symptomatic relief rather than cure for the



▲ **Figure 39–9.** Algorithm for non-ischemic priapism. (Reproduced with permission from Hudnall M, Reed-Maldonado AB, Lue TF: Advances in the understanding of priapism, Transl Androl Urol. 2017 Apr;6(2):199–206.)

underlying disease process. The pressing need to develop a cure has stimulated interest in utilizing novel treatments for ED such as stem cell (SC) therapy and low-intensity shockwave therapy. The underlying mechanisms and the short- and long-term biological effects of these therapies on the human body remain to be investigated, and well-designed rigorous studies are needed to further define the mechanisms of action, safety profiles, and efficacy of treatment in humans.

BIBLIOGRAPHY

Adeyoju AB, et al: Priapism in sickle-cell disease; Incidence, risk factors and complications - an international multicentre study. BJU Int 2002;90:898.

Althof SE, et al: Sildenafil citrate improves self-esteem, confidence, and relationships in men with erectile dysfunction: Results from an international, multi-center, double-blind, placebo-controlled trial. J Sex Med 2006;3:521.

Althof SE: Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. J Urol 2006;175:842.

Alwaal A, et al: Management of Peyronie's disease after collagenase (Xiaflex:(R)). Curr Drug Targets 2015;16:484.

Anele UA, et al: Nitrergic mechanisms for management of recurrent priapism. Sex Med Rev 2015;3:160.

Anele UA, et al: How I treat priapism. Blood 2015;125:3551.

Arafa M, et al: The prevalence of Peyronie's disease in diabetic patients with erectile dysfunction. Int J Impot Res 2007;19:213.

Araujo AB, et al: Changes in sexual function in middle-aged and older men: Longitudinal data from the Massachusetts Male Aging Study. J Am Geriatr Soc 2004;52:1502.

Aversa A, et al: The role of penile color-duplex ultrasound for the evaluation of erectile dysfunction. J Sex Med 2007;4:1437.

Bahk JY, et al: Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: Preliminary report of 7 cases. Exp Clin Transplant 2010;8:150.

Balon R: Sexual function and dysfunction during treatment with psychotropic medications. J Clin Psychiatry 2005;66:1488.

Barry JM: Priapism: Treatment with corpus cavernosum to dorsal vein of penis shunts. J Urol 1976;116:754.

Bella AJ, et al: Intracavernous pharmacotherapy for erectile dysfunction. Endocrine 2004;23:149.

Bella AJ, et al: Peyronie's disease (CME). J Sex Med 2007;4:1527.

Bodie JA, et al: Psychogenic erectile dysfunction. Int J Psychiatry Med 2003;33:273.

Brant WO, et al: T-shaped shunt and intracavernous tunneling for prolonged ischemic priapism. J Urol 2009;181:1699.

Brock G, et al: High flow priapism: A spectrum of disease. J Urol 1993;150:968.

Brock GB, et al: Efficacy and safety of tadalafil for the treatment of erectile dysfunction: Results of integrated analyses. J Urol 2002;168:1332.

Broderick GA, Kadioglu A, Bivalacqua TJ, et al: Priapism: Pathogenesis, epidemiology, and management. J Sex Med 2010;7:476.

Burnett AL, et al: Randomized controlled trial of sildenafil for preventing recurrent ischemic priapism in sickle cell disease. Am J Med 2014;127:664.

Burnett AL, et al: Feasibility of the use of phosphodiesterase type 5 inhibitors in a pharmacologic prevention program for recurrent priapism. J Sex Med 2006;3:1077.

Burnett AL, et al: Corporal "snake" maneuver: Corporoglanular shunt surgical modification for ischemic priapism. J Sex Med 2009;6:1171.

Carrieri MP, et al: A case-control study on risk factors for Peyronie's disease. J Clin Epidemiol 1998;51:511.

Carson CC, et al: Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int 2005;96:257.

Chai SJ, et al: Small-vessel lower extremity arterial disease and erectile dysfunction: The Rancho Bernardo study. Atherosclerosis 2009;203:620.

Champion HC, et al: Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. Proc Natl Acad Sci USA 2005;102:1661.

Chung E, et al: Evidence-based management guidelines on Peyronie's disease. J Sex Med 2016;13:905.

Corona G, et al: Aging and pathogenesis of erectile dysfunction. Int J Impot Res 2004;16:395.

Dean RC, et al: Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am 2005;32:379.

Deveci S, et al: Erectile function profiles in men with Peyronie's disease. J Urol 2006;175:1807.

El-Sakka AI, et al: Peyronie's disease in diabetic patients being screened for erectile dysfunction. J Urol 2005;174:1026.

Esposito K, et al: Effects of intensive lifestyle changes on erectile dysfunction in men. J Sex Med 2009;6:243.

Esposito K, et al: Dietary factors, Mediterranean diet and erectile dysfunction. J Sex Med 2010;7:2338.

Feldman HA, et al: Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 1994;151:54.

Feldman HA, et al: Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 2002;87:589.

Fernandez-Balsells MM, et al: Clinical review 1: Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560.

Fonseca V, et al: Endothelial and erectile dysfunction, diabetes mellitus, and the metabolic syndrome: Common pathways and treatments? Am J Cardiol 2005;96:13M.

Garaffa G, et al: Understanding the course of Peyronie's disease. Int J Clin Pract 2013;67:781.

Garcia MM, et al: T-shunt with or without tunnelling for prolonged ischaemic priapism. BJU Int 2008;102:1754.

Gelbard MK, et al: The natural history of Peyronie's disease. J Urol 1990;144:1376.

Georgiadis JR, et al: Human brain activation during sexual stimulation of the penis. J Compar Neurol 2005;493:33.

Giuliano F: Impact of medical treatments for benign prostatic hyperplasia on sexual function. BJU Int 2006;97(Suppl 2):34.

Glina S, et al: SOP: Corpus cavernosum assessment (cavernosography/cavernosometry). J Sex Med 2013;10:111.

Goldstein I, et al: Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. New Engl J Med 1998;338:1397.

Goldstein I, et al: A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med 2012;9:1122.

Gratzke C, et al: Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med 2010;7:445.

Gur S, et al: Current status and new developments in Peyronie's disease: Medical, minimally invasive and surgical treatment options. Expert Opin Pharmacother 2011;12:931.

Hakim LS, et al: Evolving concepts in the diagnosis and treatment of arterial high flow priapism. J Urol 1996;155:541.

Hatzimouratidis K, et al: EAU guidelines on penile curvature. Eur Urol 2012;62:543.

Hsu GL, et al: Anatomy of the human penis: The relationship of the architecture between skeletal and smooth muscles. J Androl 2004;25:426.

Huang V, et al: Bicycle riding and erectile dysfunction: An increase in interest (and concern). J Sex Med 2005;2:596.

Inman BA, et al: A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc 2009;84:108.

Jackson G, et al: The second Princeton consensus on sexual dysfunction and cardiac risk: New guidelines for sexual medicine. J Sex Med 2006;3:28.

Jin L, et al: RhoA/Rho-kinase in erectile tissue: mechanisms of disease and therapeutic insights. Clin Sci (London) 2006;110:153.

Kadioglu A, et al: A retrospective review of 307 men with Peyronie's disease. J Urol 2001;168:1075.

Kendirci M, et al: Critical analysis of surgery for Peyronie's disease. Curr Opin Urol 2004;14:381.

Kimura Y, et al: 5-HT(2C) receptor activation is a common mechanism on proerectile effects of apomorphine, oxytocin and melanotan-II in rats. Eur J Pharmacol 2008;589:157.

Kloner RA, et al: Erectile dysfunction in the cardiac patient: How common and should we treat? J Urol 2003;170:S46.

Knoll LD, et al: Physician and patient satisfaction with the new AMS 700 momentary squeeze inflatable penile prosthesis. J Sex Med 2009;6:1773.

Korenman SG: Epidemiology of erectile dysfunction. Endocrine004; 23:87.

Koseoglu N, et al, et al: Erectile dysfunction prevalence and sexual function status in patients with chronic obstructive pulmonary disease. J Urol 2005;174:249.

Kostis JB, et al: Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 2005;96:313.

Kovac JR, et al: A pathophysiology-based approach to the management of early priapism. Asian J Androl 2013;15:20.

Lagoda G, et al: Sustained nitric oxide (NO)-releasing compound reverses dysregulated NO signal transduction in priapism. FASEB J 2014;28:76.

Laties A, et al: Ocular safety in patients using sildenafil citrate therapy for erectile dysfunction. J Sex Med 2006;3:12.

Lin CS, et al: Cyclic nucleotide signaling in cavernous smooth muscle. J Sex Med 2005;2:478.

Lin G, et al: In situ activation of penile progenitor cells with low-intensity extracorporeal shockwave therapy. J Sex Med 2017;14:493.

Linet OI, et al: Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. New Engl J Med 1996;334:873.

Lue TF, et al: Should perioperative anticoagulation be an integral part of the priapism shunting procedure? Transl Androl Urol 2013;2:316.

Lue TF, et al: Summary of the recommendations on sexual dysfunctions in men. J Sex Med 2004;1:6.

Lue TF: Erectile dysfunction. New Engl J Med 2000;342:1802.

Martin C, et al: Effect of phenylephrine and terbutaline on ischemic priapism: A retrospective review. Am J Emerg Med 2016;34: 222.

McCullough AR, et al: Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. Urology 2002;60:28.

McMahon CG, et al: Disorders of orgasm and ejaculation in men. J Sex Med 2004;1:58.

Melman A, et al: Plasmid-based gene transfer for treatment of erectile dysfunction and overactive bladder: Results of a phase I trial. Isr Med Assoc J 2007;9:143.

Miner M, et al: Treatment of lower urinary tract symptoms in benign prostatic hyperplasia and its impact on sexual function. Clin Ther 2006;28:13.

Montague DK, et al: American Urological Association guideline on the management of priapism. J Urol 2003;170:1318.

Montague DK, et al: AUA guideline on the pharmacologic management of premature ejaculation. J Urol 2004;172:290.

Montague DK, et al: Chapter 1: The management of erectile dysfunction: an AUA update. J Urol 2005;174:230.

Montorsi F, et al: Summary of the recommendations on sexual dysfunctions in men. J Sex Med 2010;7:3572.

Montorsi P, et al: Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: The COBRA trial. Eur Heart J 2006;27:2632.

Morales A: Men's aging and sexual disorders: An update on diagnosis and treatment. Rev Endocr Metab Disord 2005;6:85.

Morgentaler A, et al: Testosterone therapy and cardiovascular risk: Advances and controversies. Mayo Clin Proc 2015;90:224.

Morgentaler A: Controversies and advances with testosterone therapy: A 40-year perspective. Urology 2016;89:27.

Morgentaler A: Testosterone replacement therapy and prostate risks: Where's the beef? Can J Urol 2006;13(Suppl 1):40.

Mulhall JP, et al: Congruence between veno-occlusive parameters during dynamic infusion cavernosometry: Assessing the need for cavernosography. Int J Impot Res 2004;16:146.

Mulhall JP, et al: Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol 2004;171:2350.

Mulhall JP, et al: An analysis of the natural history of Peyronie's disease. J Urol 2006;175:2115.

Musicki B, et al: eNOS function and dysfunction in the penis. Exp Biol Med (Maywood) 2006;231:154.

Mwamukonda KB, et al: Androgen blockade for the treatment of high-flow priapism. J Sex Med 2010;7:2532.

Nehra A, et al: Peyronie's disease: AUA guideline. J Urol 2015;194:745.

Nelson CJ, et al: The chronology of depression and distress in men with Peyronie's disease. J Sex Med 2008;5:1985.

Owen RT: Dapoxetine: A novel treatment for premature ejaculation. Drugs Today (Barcelona) 2009;45:669.

Papatsoris AG, et al: Erectile dysfunction in Parkinson's disease. Urology 2006;67:447.

Polsky JY, et al: Smoking and other lifestyle factors in relation to erectile dysfunction. BJU Int 2005;96:1355.

Porst H, et al: Efficacy and tolerability of vardenafil for treatment of erectile dysfunction in patient subgroups. Urology 2003;62:519.

Qian A, et al: Comparison of gene expression profiles between Peyronie's disease and Dupuytren's contracture. Urology 2004;64: 399.2004.

Quackels R: Treatment of a case of priapism by cavernospongious anastomosis. Acta Urol Belg 1964;32:5.

Roghmann F, et al: Incidence of priapism in emergency departments in the United States. J Urol 2013;190:1275.

Rosen R, et al: Impact of Peyronie's disease on sexual and psychosocial functioning: Qualitative findings in patients and controls. J Sex Med 2008;5:1977.

Rosen RC: Evaluation of the patient with erectile dysfunction: History, questionnaires, and physical examination. Endocrine 2004;23:107.

Saenz de Tejada I, et al: Physiology of erection and pathophysiology of erectile dysfunction. In: Lue T. Basson R, Rosen R, et al (eds): Sexual Medicine: Sexual Dysfunctions in Men and Women. Paris: Health Publications, Paris, 2004, p. 287.

Salonia A, et al: European Association of Urology guidelines on priapism. Eur Urol 2014;65:480.

Schwarzer U, et al: The prevalence of Peyronie's disease: Results of a large survey. BJU Int 2001;88:727.

Seftel AD, et al: Improvements in confidence, sexual relationship and satisfaction measures: results of a randomized trial of tadalafil 5 mg taken once daily. Int J Impot Res 2009;21:240.

Segal RL, et al: Corporal Burnett "Snake" surgical maneuver for the treatment of ischemic priapism: Long-term followup. J Urol 2013;189: 1025.

Segal RL, et al: Viberect penile vibratory stimulation system: Evaluation of its erectogenic efficacy. Can J Urol 2013;20:6844.

Shamsa A, et al: Erectile function in end-stage renal disease before and after renal transplantation. Transplant Proc 2005;37:3087.

Shigehara K, et al: Clinical management of priapism: A review. World J Mens Health 2016;34:1.

Sikka SC, et al: Standardization of vascular assessment of erectile dysfunction: Standard operating procedures for duplex ultrasound. J Sex Med 2013;10:120.

Smith JF, et al: Risk factors for emotional and relationship problems in Peyronie's disease. J Sex Med 2008;5:2179.

Snyder PJ, et al: Effects of testosterone treatment in older men. New Engl J Med 2016;374;611.

Soeterik TF, et al: Electroejaculation in patients with spinal cord injuries: A 21-year, single-center experience. Int J Urol 2016.

Spycher MA, et al: The ultrastructure of the erectile tissue in priapism. J Urol 1986;135:142.

Tal R, et al: Peyronie's disease in teenagers. J Sex Med 2012;9:302.

Tal R, et al: Peyronie's disease following radical prostatectomy: Incidence and predictors. J Sex Med 2010;7:1254.

Tan RB, et al: Update on medical management of Peyronie's disease. Curr Urol Rep 2014;15:415.

Tan XZ, et al: Post-traumatic high-flow priapism: Multidetector computed tomography demonstration. Urology 2015;86:e25.

Tefekli A, et al: Peyronie's disease in men under age 40: Characteristics and outcome. Int J Impot Res 2001;13:18.

Traish AM, et al: Mechanisms of obesity and related pathologies: Androgen deficiency and endothelial dysfunction may be the link between obesity and erectile dysfunction. FEBS J 2009;276:5755.

Usta MF, et al: Penile traction therapy for Peyronie's disease-what's the evidence? Transl Androl Urol 2016;5:303.

Veronelli A, et al: Prevalence of erectile dysfunction in thyroid disorders: Comparison with control subjects and with obese and diabetic patients. Int J Impot Res 2006;18:111.

Wang C, et al: ISA, ISSAM, EAU, EAA and ASA recommendations: Investigation, treatment and monitoring of late-onset hypogonadism in males. Int J Impot Res 2009;21:1.

Wolter CE, et al: The hydrophilic-coated inflatable penile prosthesis: 1-year experience. J Sex Med 2004;1:221.

Wu AK, et al: Commentary on high flow, non-ischemic, priapism. Transl Androl Urol 2012;1:109.

Yavuzgil O, et al: Endothelial function in patients with vasculogenic erectile dysfunction. Int J Cardiol 2005;103:19.

Zacharakis E, et al: Early insertion of a malleable penile prosthesis in ischaemic priapism allows later upsizing of the cylinders. Scand J Urol 2015;1.

Zacharakis E, et al: Penile prosthesis insertion in patients with refractory ischaemic priapism: Early vs delayed implantation. BJU Int 2014;114:576.

This page intentionally left blank

Women’s Sexual Health

40

Alan W. Shindel, MD, MAS; &
Tami S. Rowen, MD, MS

INTRODUCTION

In 1897, the physician Robert Taylor stated “in the case of a woman performance of the sexual act, at least so far as her partner is concerned, requires only the presence of a sufficiently long and patulous mucous canal.” Dr. Taylor went on to discuss some aspects of female sexuality and means to improve upon women’s sexual satisfaction. However, he concluded that for many women “pleasure in the sexual act is not to be excited; nor is this to be regretted, since such women make good wives, loving mothers, and are not tempted to stay in the paths which the comparatively small number of their more amorous sisters at times find too alluring” (Taylor, 1897).

While we may be nonplussed at the quaint misogyny of Taylor’s statements, the fact remains that over 120 years later the medical communities understanding of, and interest in, female sexuality lags far behind that of our understanding of men’s sexuality. There are numerous potential reasons for this disparity; however, it is no longer acceptable to justify that disparity on the outmoded concept that women’s sexuality is simply more complex then men’s and is therefore inscrutable (Shindel and Goldstein, 2016).

SEXUAL WELLNESS

The concept of sexual wellness has been described as (WHO, 2006)

1. A state of physical, emotional, mental, and social well-being in relation to sexuality
2. Not merely the absence of disease, dysfunction, and/or infirmity
3. An important and integral aspect of human development and maturation
4. A human right

Physical and psychological issues may impair sexual wellness and diminish quality of life (Davison et al, 2009). As treatment of biomedical problems fall within the expertise of healthcare providers, these issues merit close consideration during medical consultations. While these physical and mental issues may be the principal focus of healthcare providers, it is important that the emotional and cultural aspects of sexuality be considered when providing advice and care to any individual with sexual concerns.

Sexuality concerns are not infrequent in women presenting for urologic care; furthermore, sexual interest and activity persists at least into the ninth decade for some women (Elsamra et al, 2010; Waite et al, 2009). However, urologists and other providers rarely consider these issues during routine practice (Bekker et al, 2009; Sobecki et al, 2012). It behooves all practicing physicians, particularly those who provide care for women’s urological and gynecological issues, to be well versed in the physiology and pathophysiology of female sexuality (Shindel and Goldstein, 2016).

FEMALE SEXUAL RESPONSE

Human sexual response is modulated by a complex interplay of neurological, vascular, hormonal, and sociocultural factors (Schober and Pfaff, 2007). Classically, sexual responses were categorized as a linear process of desire, arousal, sexual plateau, orgasm, and resolution (Kaplan, 1977; Masters and Johnson, 1966). Each phase of sexual response is associated with physical and mental changes (Table 40–1).

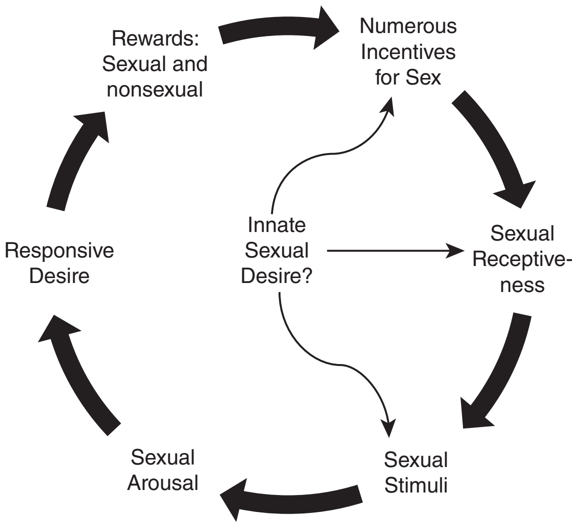
The linear model applies well in most men, but its applicability to women is more variable. Some women rarely, if ever, experience intrinsic sexual desire but may be highly receptive to sexual initiation by a partner (Basson, 2002). Some women may also experience satisfying sexual encounters without orgasm, whereas other women may be multiply orgasmic during a single sexual encounter (Bancroft and Graham, 2011). This variability is not a de facto indication of pathology in any given women but does necessitate inquiry on what is typical and satisfactory for a given woman presenting for sexual wellness consultation.

Table 40–1. Physical and mental aspects of the sexual response cycle.

Phase	Genital changes	Nongenital changes
Arousal	Vulvar and clitoral swelling, vaginal lubrication and lengthening, increased genital sensitivity	Nipple erection, tachycardia, tachypnea, subjective pleasure and excitement
Plateau	Maintenance of arousal phase genital changes	Steadily enhancing sexual excitement and pleasure
Orgasm	Involuntary, rhythmic congrations of the pelvic musculature, uterine and anal contractions, myotonia	Intense pleasure with altered state of consciousness, accompanied by sense of well-being and contentment
Resolution	Reduction of pelvic blood flow, cessation of lubrication, vulva and clitoris return to baseline	Relaxation of nipple erection, restoration of heart and respiratory rate to baseline, Decreased sexual interest

Data from Masters WH, Johonson VI: Human Sexual Response. Boston MA: Little, Brown & Company; 1966.

In part because of limitations of the linear model, some experts have advocated a "circular" model of sexual response that attempts to encompass the emotional and relational aspects of sexual response and satisfaction (Figure 40–1) (Basson, 2002). In survey studies, this circular model is endorsed by a significant minority of women as being more reflective of their sexual responses. Interestingly, these women tend to score lower on commonly utilized instruments for the assessment of sexual response (eg, the Female Sexual Function Index [FSFI]) (Giles and McCabe, 2009; Sand and Fisher, 2007). It is not clear whether this represents genuinely poorer sexual response in women who identify with the circular model or a deficiency of standard validated instruments for the assessment of sexuality in this subset of women. It may be hypothesized that the secondary gains from sexual activity (eg, emotional intimacy, fostering relationship) that are highlighted in the circular model may be key drivers of sexual response in women who have lower intrinsic desire, decreased arousal, and/or infrequent orgasms during partnered sex (Shindel and Goldstein, 2016).



▲ **Figure 40–1.** Circular Sexual Response Model. (Data from Basson R. A model of women's sexual arousal, J Sex Marital Ther. 2002 Jan-Feb;28(1):1–10.)

ANATOMY

An understanding of relevant genital anatomy is crucial to understanding female sexuality. The **vulva** is the most appropriate collective term for the external-most portion for the female genital tract. The **labia majora** are paired organs that extend from the mons pubis to the perineum; these structures contain sebaceous glands and keratinized (O'Connell et al, 2008). Between the labia majora are the paired **labia minora**, which are nonkeratinized networks vascular tissue in fibrous stroma (Yang et al, 2006). The **vestibular** (also termed **Bartholin's**) **glands** are located near the labia majora and are responsible for production of lubricating fluid. There is marked variability in labial appearance between women (Lloyd et al, 2005); this is rarely a source of physical/sexual concern but may cause cosmetic concerns for some women (Herbenick et al, 2011). Education on normal variation may assuage many women's concerns (Shindel and Goldstein, 2016).

The **vulvar vestibule** is a nonkeratinized mucosal tissue between the labia minora and is immediately adjacent to the **vaginal introitus**. The **vagina** is a tube-shaped, elastic, muscular organ that is in most circumstances a potential space. The vagina extends from the vulvar vestibule at the level of the hymen to the **cervix** (O'Connell et al, 2008). The submucosal lamina propria of the vagina contains a rich vascular innervation that permits engorgement and expansion during sexual arousal (O'Connell et al, 2008; Musicki et al, 2009). With vasodilation, oncotic pressures lead to a liquid transudate through aquaporins located within the vaginal mucosa cells (Martin-Alguacil et al, 2006; Munarriz et al, 2002; Park et al, 2008). This fluid is responsible for vaginal lubrication associated with sexual arousal; there are no glandular elements within the vagina (Woodard and Diamond, 2009).

The **clitoris** consists of two erectile bodies that are attached bilaterally to the ischium lateral to the vagina (Mazloomdoost and Pauls, 2015). The externally visible portion of the clitoris is known as the **glans** and is often obscured by the confluence of the superior portion of the labia minora (**clitoral prepuce**) (O'Connell et al, 2008). The majority of the clitoris is internal and immediately superior to the vagina. During sexual arousal the erectile tissue of the clitoris engorges with blood. The erectile tissue of the clitoris is surrounded by a fibroelastic sheath called the **tunica albuginea**. The tunica of the clitoris is thin relative to the tunica of the penis; thus, the venocculsive capacity of the clitoris is less than that of the penis and during arousal the clitoris typically will not become rigid (Yang et al, 2006).

The **clitoral bulbs** are posterior and caudad to the clitoris and consist of paired bilateral organs that surround the vagina. Despite their proximity to the glans clitoris, the clitoral bulbs do not appear to merge with it. These organs consist of erectile tissue but do not have a tunica albuginea; as such, they may engorge with blood but do not become firm during sexual arousal (O'Connell et al, 2008; Yang et al, 2006).

In 1950 Dr. Ernst Graffenberg postulated the existence of an area of the anterior vagina that was associated with intense sexual pleasure with stimulation. This area has been dubbed the "G-spot" in Dr. Graffenberg's honor (Goldberg et al, 1983). Although some women self-report intense pleasure from stimulation of this area, anatomical and imaging studies have been inconsistent in terms of demonstrating a discrete gland or organ in the purported location of the G-spot (O'Connell et al, 2008). The existence (or lack thereof) of the G-spot is likely to remain somewhat controversial. On a practical level, women should be encouraged to explore for themselves whether stimulation of the purported G-spot (or any other part of her body) is particularly pleasurable. The existence of a specific structure or tissue is less relevant than the personal question of whether a given woman finds G-spot stimulation arousing.

The **urethra** is not a sexual organ but is of obvious importance to urologists. The **urethral meatus** is located between the clitoris and vaginal introitus; the proximity of the urethra to the vagina and clitoris makes urethral pathology and/or surgeries highly relevant to sexuality (Yang et al, 2006).

NEUROVASCULAR PROPERTIES OF THE EXTERNAL GENITALIA

The nerve supply of the labia majora is derived from the anterior labial branch of the ilioinguinal nerve and posteriorly from the labial branch of the pudendal nerve. The blood supply of the labia majora and minora comes from labial branches of the external pudendal artery, which is derived from the femoral artery. The external labial veins drain to the great saphenous vein (O'Connell et al, 2008).

The external genitalia and urethra are further innervated by the **perineal neurovascular bundles**, which are branches of the pudendal nerve and originate near the takeoff point of the clitoral nerves.

The clitoris has extensive nerve and blood supply. The principal blood supply to the glans clitoris is via the dorsal clitoral arteries, which are branches of the pudendal arteries. Additional blood supply is derived from perineal arteries (bulbar and urethral branches) and the deep arteries of the clitoral bodies, which primarily feed the erectile bodies of the clitoris. The clitoral prepuce derives its blood supply from the external pudendal arteries (O'Connell et al, 2008). The deep dorsal vein drains the erectile tissues of the clitoris (O'Connell et al, 2008).

The dorsal clitoral nerves are derived from the pudendal nerve and originate near the pelvic side wall. These nerves extend along the surface of the clitoral tunica but most terminate in the glans clitoris.

The dorsal nerve of the clitoris is the principal somatic sensory innervation of the clitoris and surrounding tissues (O'Connell et al, 2008). These fibers are positive for and cholinergic and nitergic neurons, which innervate erectile tissue (Yucel and Baskin, 2004). The glans clitoris only stains positive for substance P and CGRP, indicating that its main role is sensory. Nerve endings in the glans clitoris include free nerve endings (sensitive to temperature and light touch) and Pacini's corpuscles (sensitive to vibration and pressure) (O'Connell et al, 2008; Martin-Alguacil et al, 2006).

HORMONES AND THE GENITALS

It is well established that vaginal tissue and vulvar tissue have numerous estrogen receptors (Martin-Alguacil et al, 2006). Several studies have demonstrated a positive effect of local estrogen therapy for women who have sexual pain and dryness related to estrogen deficiency (Sarrel, 2000). The vaginal vulvar tissue also is also rich in androgen receptors (Hodgins et al, 1998). Androgen deficiency states have been linked to deleterious effects in female genital tissues, although this relationship is not as well defined as that of estrogens (Martin-Alguacil et al, 2006).

EVALUATION OF SEXUAL WELLNESS IN WOMEN

History

Sexual health inquiry is relevant to urologists and other providers who provide healthcare for women. Many patients are hesitant to discuss these issues with healthcare providers because of embarrassment, a sense of futility, notions that sexuality is not a medical concern, or simple lack of time during consultations (Nicolosi et al, 2006). As patients may be hesitant to broach the topic, it is essential that healthcare providers proactively inquire about the patient's sexual concerns (Hatzihristou et al, 2016). The method for initiating inquiry can be left to the discretion of the provider, but simple, open-ended inquiries that avoid assumptions about sexual relationships, activity, and orientation are preferred. An example would be "What concerns or questions do you have about sexuality?" (Kingsberg and Althof, 2009). Normalizing statements (eg, "I ask all of my patients about sexual wellness" or "Many patients have sexual concerns") may help patients feel at ease about discussing this sensitive topic (Sadovsky and Nusbaum, 2006). Alternatively, simple survey instruments may be used as a screening questionnaire (Clegg et al, 2012). Although these tools may help identify patients with sexuality concerns, they cannot take the place of a detailed inquiry by a concerned health care provider (Kingsberg and Althof, 2009; Clegg et al, 2012).

A woman reports concerns related to sexuality, follow-up questions should be asked. Sexual, medical, relational, and emotional aspects should be explored (Basson et al, 2010). The nature of the concern (chief concern, associated symptoms, onset, related factors, previous treatments) should be carefully elucidated (Kingsberg and Althof, 2009; Basson et al, 2010). It is prudent to avoid assumptions about the patient's partner or sexual relationship status until the patient reveals this information; inquiries on these matters should be kept nonspecific (eg, with avoidance of gender-specific pronouns) (Shindel and Goldstein, 2016). While assumptions about the partner should be avoided, an understanding of the patient's relationship dynamic is essential as sexual distress is highly correlated to strife with her partner(s) (Witting et al, 2008).

Physical Examination

A general physical examination is warranted to screen for conditions that are commonly comorbid with sexuality concerns (Basson et al, 2010). A thorough and careful pelvic examination is of critical importance. Pelvic examination should include assessment of vaginal pH, inspection within labial folds, and a thorough bimanual evaluation with a focus on the pelvic floor. Evaluation of the external genitalia may reveal lesions, anatomical variants, tissue atrophy, dermatological conditions, or other anomalies that may predispose to sexual concerns (Goldstein and Alexander, 2005). Simple methods to test for neural integrity (eg, application of heat/cold, vibration sensation, or sharp sensation) may be applied. A simple cough or Q-tip test may reveal urinary concerns that contribute to sexual distress (Goldstein and Alexander, 2005). Although difficult to detect on physical exam, urethral diverticulum is a frequently missed cause of dyspareunia, dysuria, and urinary dribbling (the "3 Ds") (Antosh and Gutman, 2011). Assessment of the obturator internus, levator ani, and bulbocavernosus muscles may reveal point tenderness and/or pelvic floor laxity or hypertonicity, any of which may contribute to sexual concerns (Rosenbaum and Owens, 2008). In some cases a speculum examination may be warranted (eg. if there are complaints related to the vagina or deep pelvic pain during sex) (Goldstein and Alexander, 2005).

Adjunctive Tests

The utility of serum studies for sexual concerns in women is somewhat ambiguous. Chemistry, lipids, and glycosylated hemoglobin are routine labs that may be of some value. Assessment of estrogen levels should be considered if there are signs of estrogen deficiency; however, these assays are less helpful during perimenopause, given their wide variation (Burger et al, 2008). Phase of the menstrual cycle is essential information for interpretation of estrogen levels in premenopausal women (Kingsberg and Althof, 2009). If estrogen levels are determined to be abnormal, repeat assessment with adjunctive labs including prolactin, follicle-stimulating hormone, and leutinizing hormone may be of utility (Kingsberg and Althof, 2009; Atis et al, 2010). Assessment of serum testosterone is advocated by some experts; however, testosterone levels can be difficult to quantify at the levels commonly found in women, and the clinical utility of this information is controversial (Bancroft and Graham, 2011).

Advanced laboratory testing (biothesiometry, vaginal plethysmography, color Doppler ultrasound) is useful in research settings, but the precise role for these technologies in routine practice is as of yet unclear (Woodard and Diamond, 2009; Chivers et al, 2010). Advanced imaging with computed tomography or magnetic resonance imaging may be warranted in some select cases where a specific anatomic pathology is suspected (eg, urethral diverticulum) (Suh et al, 2003). However, in most cases a thorough physical examination by an experienced provider can elucidate the relevant physical findings.

Referral

Appropriate referral should be initiated if the problem is outside the scope of practice of the healthcare provider (Goldstein and Alexander, 2005). This referral should be to a colleague with expertise in sexual medicine. Consultation with a mental health or relationship professional is also valuable as most sexual issues involve a psychoemotional component. A therapist with expertise and interest in sexuality is preferred as not all therapists are expert at evaluating the complex psychological issues surrounding sex (Althof, 2010; McCabe et al, 2010). While referral to a mental health specialist is very valuable, it should be made clear to the female patient that this referral is part of a comprehensive approach to sexual wellness and does not imply that the problems are "all in her head"…careful attention to biological parameters (anatomical, hormonal, etc) is also critical.

Special Populations

Sexual activity during pregnancy is generally regarded as safe (Millheiser, 2012). However, certain sexual activities and/or positions may become difficult or even impossible, particularly during the later stages of pregnancy. Caution must also be exercised when considering vaginal penetrative sexual activity in women with cervical incompetence or other risk factors for preterm labor. Labor is associated with significant risk of injury to the vagina and perineum, any of which may lead to postdelivery sexual concerns (Leeman and Togers, 2012; Pauls et al, 2008). However, there are currently insufficient data to clearly demonstrate a definite relationship between mode of delivery (ie, vaginal versus Caesarean section) and postpartum sexual function (Leeman and Rogers, 2012).

Women who choose to breastfeed will experience robust production of prolactin, which may have a suppressive effect on sex steroids and resultant impact on libido and genital tissues. These suppressive factors may exacerbate the psychological stressors and time demands that are common impediments to sexuality for parents of neonates (Leeman and Rogers, 2012; Pauleta et al, 2010).

Sexuality is tightly bound in sociocultural mores; perceptions of what constitutes normal and acceptable forms of sexual expression for women will have a strong influence on how a woman perceives her sexuality and sexual responses (Anderson et al, 2011). Cultural factors may explain in part the widely divergent prevalence for various sexual concerns around the world (Laumann et al, 2005). It is not the purpose of providers to dictate how a woman relates to her sexuality; however, a level of respect and willingness to understand the woman's feelings about her sexual experience is essential. Providers are also well advised to remember that there is a diversity of opinions on sexuality within demographic groups (eg, some women from conservative communities may personally hold liberal sexual beliefs, and vice versa) and that sexual self-determination is considered a human right (WHO, 2006).

Women who have sex with women (WSW), transgendered individuals (both female-to-male and male-to-female), and other persons who reject gender labels have been poorly represented in the biomedical research literature on sexual function. However, the prevalence of lifetime same-gendered sexual activity is not insignificant in women, even among individuals who identify as heterosexual (Burri et al, 2012; Xu et al, 2006). Conversely, many women who identify as lesbian also report lifetime and even current sexual activity with men (Diamant et al, 1999). The nature of sexual activity in WSW dyads is highly variable, and there is evidence that WSW generally have a greater variety of sexual experiences (Burri et al, 2012; Xu et al, 2006). The prevalence and associations of sexual problems in WSW appear generally similar to what is reported in women who have sex with men (MSM), although the impact of these issues may differ (Shindel et al, 2012). It is important that providers who are generally unfamiliar with WSW take the time to understand the particular concerns of a given patient and ask (respectfully) for clarification of issues that are not clear (Stott, 2013). This willingness to listen and understand is of particular importance when caring for transgendered patients, who may (or may not) have concerns regarding hormone replacement or surgical gender reassignment (Makadon, 2011). These topics may have profound and important impacts on sexual expression.

Disability is broadly defined as a mental and/or physical condition (acquired or congenital) that may limit an individual's capacity to function independently and/or without assistance. Disability is not a contraindication to sexual expression and enjoyment; adaptive processes and/or incorporation of alternative means of sexual gratification may be of great benefit to disabled persons (Rowen et al, 2015). Mental disability does demand careful and individualized consideration as there is a very real potential for abuse or coercion in persons who have difficulty granting or even understanding the concept of consent (Kennedy, 2003). Mentally disabled persons should not be denied the right to sexual pleasure, but safeguards must be in place to optimize the person's ability to express her/his free will regarding sex (Spieker and Steutel, 2002; Greenspan, 2002).

Gender-based violence and sexual assault are unfortunately very common problems worldwide (WHO, 2013). The high prevalence of these crimes mandates that providers be sensitive to the fact that many female patients they encounter will have been victims. Aside from the potential for physical injury to the genitals, the long-term psychological consequences of sexual violence may exert a very strong and negative impact on sexual expression (Schulte-Herbruggen et al, 2009). Attentive and respectful medical and possibly mental health consultation may be necessary to address these issues; the intention of therapy is to empower the woman to feel in control of her sexuality and to dissociate consensual sex from the prior assault (Basson et al, 2010).

Urogynecological conditions (eg, urinary incontinence, interstitial cystitis) may be the cause or side effect of sexual concerns (Chen et al, 2013). Treatment (medical or surgical) for urogynecological conditions has the potential to either improve or exacerbate sexual concerns in women (Chen et al, 2013; Wehbe et al, 2017). Transvaginal mesh placed for incontinence pelvic organ prolapse may have either positive or negative impacts on sexual enjoyment (Altman et al, 2009; Roovers et al, 2006). Similarly, hysterectomy has been associated with both positive and negative consequences for sexual function in women; the likelihood of either seems largely predicated on the indication for the procedure (Roovers et al, 2003; Greer et al, 2010). Women who are experiencing sexual concerns related to their urogynecological condition may be more likely to report overall improvement post-intervention. Women who are undergoing surgery for malignancies of the pelvis will often experience marked declines in sexual function (Donovan et al, 2010; Raina et al, 2007); this may relate to surgical or radiotherapy ablation of pelvic organs, side effects of adjunctive chemotherapy and/or hormonal therapy, and the psychological burden of a cancer diagnosis (Incrocci and Jensen, 2013; Zippe et al, 2004).

FEMALE SEXUAL DYSFUNCTION

Female sexual dysfunction (FSD) has been referred to as a diagnosis in many publications on women's sexuality. The acronym FSD is more accurately defined as a comprehensive term that refers to one or more specific distressing situations that impair a woman's capacity for sexual enjoyment.

The best overall predictor of sexual distress in women is the quality of the emotional relationship with her partner (Bancroft et al, 2003). Physical issues play a role and may be of primary concern for some women, but in general relationship issues appear to be primary determinants of overall sexual satisfaction for most women. This relationship underscores how physical disruption of sexual response and sexuality-related distress may often occur independently of one another in women (Shifren et al, 2008). In an attempt to address this issue, Raina et al (2007) proposed a tripartite classification system:

1. **Sexual complaints:** Expressions of discontent with sexual function, often related to partner or personal issues around sexual experience.
2. **Sexual dysfunction:** Disruption of one or more phases of sexual response, often related to physical issues. Some women may be able to adapt to these with minimal disturbance in sexual satisfaction and as such may not require extensive biomedical intervention.
3. **Sexual disorder:** The combination of a sexual dysfunction and related personal distress. These conditions merit close assessment and intervention.

The concept of FSD has sparked an impassioned and sometimes bitter debate in a way that discussion of men's sexual function never has. Critics have contended that concepts of FSD are deeply rooted in male-centric concepts of sexuality (Basson, 2002), or that psychosocial factors are of sufficiently greater relevance to sexual satisfaction in women than biological factors and that biological inquiry is of little importance (Tiefer, 2002, 2007), or even that the concept of FSD is simply an attempt for financial gain on the part of the healthcare industry (Tiefer, 2002; Moynihan, 2004). While all of these arguments must be taken seriously, it remains the case that sexuality is very much a physical (and emotional) phenomenon and that healthcare providers are the most qualified to address the physical aspects of sexuality in women. In the ideal situation, sexual health consultation is tailored to the patient's unique needs and will incorporate biomedical, mental health, and interpersonal interventions as warranted (Basson et al, 2010). Fundamentally, the opportunity to discuss sexuality in an open and nonjudgmental fashion with a professional may substantially alleviate sex-related distress for many women, even in the absence of other interventions (Goldstein and Alexander, 2005).

CLASSIFICATION

The most widely utilized classification system for female sexual disorders is the Diagnostic and Statistical Manual of Mental Disorders (DSM), currently on its fifth edition (DSM-V), which was published in May 2013 (APA, 2013). Currently, the DSM recognizes **female sexual interest/arousal disorder** (a synthesis of the prior DSM diagnoses of **hypoactive sexual desire disorder** and **female sexual arousal disorder**), **female orgasm disorder**, and **genito-pelvic pain/penetration disorder** (a synthesis of the prior DSM diagnoses of **dyspareunia** and **vaginismus**) (APA, 2013). To qualify as a diagnosis, the DSM-V stipulates that the condition must cause personal distress, be present in at least 75% of sexual encounters, and of at least 6 months' duration. These diagnoses are further characterized as mild versus moderate versus severe, lifelong versus acquired, and situational versus generalized (APA, 2013).

There is scant empirical or research data on the new DSM-V classification scheme. As such, the International Society for the Study of Women's Sexual Health and the International Consultation on Sexual Medicine have promoted definitions for sexual concerns that are more closely aligned with definitions from existing data (Parish et al, 2016). Importantly, this classification scheme does not include sexual pain disorders; these are encompassed in the 2015 consensus classification of persistent vulvar pain and vulvodynia (Bornstein et al, 2016). These definitions will be used for the remainder of this chapter. The various classification systems are presented in Table 40–2.

Hypoactive Sexual Desire Disorder

Hypoactive sexual desire disorder (HSDD) is defined as a lack of motivation for sexual activity manifested by either reduced/absent spontaneous desire or reduced/absence responsive desire to erotic cues and stimulation *or* loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity (Parish et al, 2016). It is important to note that sexual desire/arousal can be an end unto itself and can be perceived positively even in the absence of sexual activity (Wallen and Lloyd, 2011). Therefore, attention to issues of sexual desire may yield benefit even in women who do not report related changes in sexual events.

The prevalence of HSDD is estimated at around 10% (Shifren et al, 2008). Common associations include issues with a sexual partner, declines in serum sex steroids (estrogen and testosterone), life stressors, and antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs) (Brotto et al, 2011; Clayton et al, 2012). Some women using hormonally based contraception report bothersome declines in sexual interest; this may relate to declines in production of testosterone and increased production of sex-hormone-binding globulin (SHBG) (Burrows et al, 2012).

Management of HSDD is driven in large part by the nature of the concern and associated issues. In women taking antidepressant medications, cessation, dose reduction, and/or selection of an alternative agent may play an important role in improving these symptoms (Burrows et al, 2012; Clayton and Montejo, 2006). Such interventions should be done only by a provider who is comfortable with adjusting antidepressant regimens. Adjunctive therapy with either bupropion or buspirone has been reported to mitigate SSRI-related declines in sexual desire (Taylor et al, 2013; Landen et al, 1999).

Estrogens have not demonstrated convincing efficacy for management of isolated HSDD (Wierman et al, 2010).

Table 40–2. Classification of female sexual dysfunctions.

	Diagnostic and statistical manual, 4th edition text revision	Diagnostic and statistical manual, 5th edition	International society for the study of women's sexual health/International consultation on sexual medicine
Disorders of Sexual Desire	**Hypoactive Sexual Desire Disorder:** Persistent or *recurrently* deficient (or absent) sexual *fantasies* and desire for sexual activity. The judgement of deficiency or *absence* is made by the clinical, taking *into* account factors that affect sexual functioning, such as age and the context of the person's life **Sexual Aversion Disorder:** Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner	**Female Sexual Interest/Arousal Disorder***:* Three or more of the following symptoms are manifested. These include the absence of an interest in sexual activity; or a decided reduction of such; and an absence of fantasizing or even thinking sexual or erotic thoughts. As well, the female is disinclined to initiate sexual encounters with her partner; and exhibits no sense of pleasure during sexual acts.	**Hypoactive Sexual Desire Disorder:** Lack of motivation for sexual activity as manifested by either (1) reduced or absent spontaneous desire (sexual thoughts or fantasies) or (2) reduced or absent responsive desire to erotic cues; and stimulation or inability to maintain desire or interest through sexual activity OR loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders
Disorders of Sexual Arousal	**Female Sexual Arousal Disorder:** Persistent or current inability to attain, or to maintain until completion of sexual activity, an adequate lubrication-swelling response of sexual excitement **Persistent Genital Arousal Disorder** is not specifically defined	**Persistent Genital Arousal Disorder** is not specifically defined	**Female Genital Arousal Disorder:** the inability to develop or maintain adequate genital response including vulvovaginal lubrication, engorgement of the genitalia and sensitivity of the genitalia associated with sexual activity **Persistent Genital Arousal Disorder:** persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal or being on the verge of orgasm (genital dysesthesia), not associated with concomitant sexual interest, thoughts or fantasies
Disorders of Orgasm	**Female Orgasm Disorder:** Persistent or recurrent reduction in, or absence of, orgasm following a normal sexual excitement phase.	**Female Orgasm Disorder:** a significant change in orgasm such as delay, reduction of intensity or cessation	**Female Orgasmic Disorder:** persistent or recurrent, distressing compromise of orgasm frequency, intensity, timing, and/or pleasure, associated with sexual activity ***Pleasure Dissociative Orgasm Disorder:** Orgasm occurs with decreased or absent pleasure ***Female Orgasmic Illness Syndrome:** Peripheral and/or central adverse symptoms that occur before, during, or after orgasm not related, per se, to a compromise of orgasm quality
Sexual Pain Disorders	**Dyspareunia:** Recurrent or persistent genital pain associated with sexual intercourse **Vaginismus:** Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse	**Genitopelvic Pain/Penetration Disorder:** A condition in which the pelvic floor muscles around the vagina contract or tighten whenever an attempt is made to penetrate	Sexual Pain Disorders are not grouped with the ISSWSH/ICSM sexual disorders. The International Society for the Study of Vulvovaginal Diseases, the International Pelvic Pain Society, and the International Society for the Study of Women's Sexual Health characterize vulvar pain as either **"Vulvar Pain caused by a specific disorder"** or **"Vulvodynia"** when no clear identifiable cause can be determined. Dyspareunia is pain during sexual activity related to either of these

*These diagnoses are based on expert opinion and as such should be considered provisional until such time as further data become available.

Data from DSM IV-TR 2000, DSV-V 2013, Parish 2016, Bornstein 2016.

However, postmenopausal women using estrogen-based hormone replacement are more likely to be sexually active (Gass et al, 2011), and estrogen replacement has been associated with improvement in sexual desire (Gast et al, 2009). This effect may be mediated by direct action on libido or indirectly by improving genital atrophy and responsiveness. Androgens have also been advocated by some experts for normally estrogenized women with persistent HSDD (Shifren et al, 2008). Androgens are not currently approved for any indication in women, and measurement/dosing can be a challenge in female patients. Many women have concerns about the long-term safety profile of hormone replacement therapy, based mainly on the initial findings of the women's health initiative, the results of which have shown far more safety than initially presented (Rossouw et al, 2013). The data on androgen replacement have focused mainly on the role of transdermal testosterone supplementation. Androgen replacement has been shown to have beneficial effects on desire as well as increased sexual activity (Davis SR et al, 2016). The main limitation to use is the lack of an FDA-approved formulation and concerns over long-term safety effects. The data, however, do suggest that testosterone used in physiologic doses does not increase risk of heart disease or uterine cancer. There are very limited data on breast cancer risk related to testosterone supplementation in women (Davis SR et al, 2015).

Flibanserin is a 5-HT_{1A} receptor (Gelez et al, 2013). This agent was investigated as an antidepressant but did not provide statistically meaningful improvements for this condition. However, there were slight but noticeable improvements in sexual function for women using the compound in these studies. Subsequent validation studies of flibanserin indicated that the drug was substantially superior to placebo for management of distressing HSDD in both premenopausal and postmenopausal women (Katz et al, 2013; Simon et al, 2014; Thorp et al, 2012). The US Food and Drug Administration (FDA) mandated that a primary endpoint of the trials be "satisfying sexual events" per month. Flibanserin was associated with a marginal increase in SSE compared to placebo. However, it must be remembered that the indication for this drug is not absence of SSE but rather HSDD; in terms of enhancing sexual desire and sense of oneself as a sexual being, flibanserin performed well compared to placebo.

After being rejected by the FDA in 2010 and 2013, flibanserin was finally approved for use in 2015. Currently, it is available by prescription. It is recommended that flibanserin not be taken within 2 hours of consuming alcohol; an earlier prohibition of alcohol consumption in the context of flibanserin use was based on studies in which young men took the medication and drank two alcoholic beverages in 10 minutes (FDA, 2015). The actual blood pressure effects of flibanserin and alcohol appear mild (Stevens 2017).

Positive lifestyle changes (eg, weight loss, exercise) have been convincingly linked to positive changes in male sexual function (Esposito et al, 2010a), but evidence of similar effects in women is less robust; however, an Italian study did demonstrate that a diet low in processed foods and saturated fats was associated with lower prevalence of sexual arousal disorders in diabetic women (Esposito et al, 2010b). Positive lifestyle changes may also exert beneficial sexual effects from improved body image and exercise tolerance. Even in the absence of potential sexual benefits, healthy levels of activity and a prudent diet should be encouraged for all patients because of the general health benefits of such types of intervention.

Female Genital Arousal Disorder

Female genital arousal disorder (FGAD) is defined as an inability to develop and/or maintain adequate genital response, including vulvovaginal lubrication, genital engorgement, and/or sensitivity of the genitalia associated with sexual activity (Parish et al, 2016). It is important to note that the diagnosis of FGAD applies only in situations where the woman is receiving sexual stimulation that is adequate and appropriate in focus, intensity, and duration. The situation in which a woman does not become aroused because of insufficient sexual stimulation would not necessarily qualify as FGAD unless this represented a marked decline from prior (Parish et al, 2016).

The estimated prevalence of distressing FGAD is approximately 5% (Shifren et al, 2008). As with many other sexual problems in women, psychorelational issues have been shown to be strongly associated with disruptions of arousal (Basson et al, 2010). Hormonal deficiencies, particularly declines in estrogen that may be associated with menopause (surgical or natural), have also been associated with genital atrophy and declines in baseline genital moisture; these may contribute to poorer arousal (Bachmann et al, 1999). Animal models and human epidemiological studies have suggested that vascular or neurological disease may lead to FGAD (Giraldi and Kristensen, 2010; Traish et al, 2010). Interestingly, there are data to suggest that arousal responses in postmenopausal women may be largely intact, presuming adequate sexual stimulation (Brotto and Gorzalka, 2002). This suggests that for some postmenopausal women, more protracted sexual stimulation may mitigate some issues of poor arousal response. Additional risk factors for FGAD include pelvic surgery, nicotine, and metabolic diseases such as diabetes (Raina et al, 2007; Giraldi and Kristensen, 2010; Harte and Meston, 2008).

Attention to underlying psychological conditions is often of great importance in management of GFAD. Hormonal factors, most commonly hypoestrogenism or hypoandrogenism, are also frequently implicated in FGAD, and appropriate supplementation may help mitigate these concerns (Bachmann and Oza, 2006). Specific therapies include estrogens (systemic or local to the vagina), selective estrogen receptor modulators (SERMs), and the synthetic hormone tibolone (Gast et al, 2009). Androgen supplementation may be considered for some women, but this therapy is not currently approved for use in women within the United States; this should be considered only after a detailed conversation of the risks and benefits between the patient and a provider who is highly knowledgeable about androgen supplementation in women.

Genital moisturizers (used routinely to promote vaginal moisture) and lubricants (used at the time of sexual encounters) may overcome some issues with impaired genital responsiveness in women (Herbenick et al, 2011). A detailed analysis of lubricants is beyond the scope of this chapter, but various options exist. Use of sexual enhancement devices (vibrators, sexual toys, devices for sensation play) may enhance arousal responses for many women. Use of such devices has been associated with improved scores on the FSFI (Heerbenick et al, 2010). While most such items are safe if used properly, many are marketed as "novelties" and as such may not be manufactured according to optimal safety standards. Patients should exercise caution to avoid injury or loss of such devices in body cavities from inappropriate use of poor-quality devices (Aaronson and Shindel, 2010).

There are no pharmacotherapies currently approved by the FDA for the treatment of FGAD. There was initially intense interest in medications of the phosphodiesterase type 5 inhibitor (PDE5I) class for this indication. These medications have been used to great effect in men with arousal disorder (eg, erectile dysfunction [ED]), but similar studies in women with FSD have yielded negative results (Basson et al, 2012). However, in women with precisely characterized etiologies for impaired arousal (eg, spinal cord injury, multiple sclerosis, diabetes), PDE5I has been associated with some degree of efficacy (Caruso et al, 2006; Dasgupta et al, 2004; Sipski et al, 2000). Alternative pharmotherapeutic options include topical prostaglandins (applied the clitoris or labia); these interventions appear to aid some women with arousal disorders, but there is some potential for side effects such as genital irritation (Liao et al, 2008).

Persistent Genital Arousal Disorder

Persistent genital arousal disorder (PGAD) is a poorly understood and somewhat rare condition characterized by persistent or recurrent, unwanted, distressing feelings of genital arousal or feelings of being on the verge of orgasm not associated with concomitant sexual interest, thoughts, or fantasy. PGAD is often refractory or only partially mitigated by orgasm. The psychological stress of these unrelenting feelings can be quite severe, leading some women to report contemplating suicide (Parish et al, 2016).

As the condition is poorly understood, conditions that are commonly associated with PGAD are difficult to characterize. PGAD has been associated anecdotally with arteriovenous malformations, epilepsy, restless-leg syndrome, overactive bladder, changes in hormone therapy, pudendal nerve entrapment, and certain antidepressants. However, many cases are simply idiopathic (Garvey et al, 2009; Leiblum et al, 2007; Waldinger and Schweitzer, 2009).

A detailed history and physical examination by a provider experienced in management of PGAD is essential. If a precipitating factor (eg, medication, diagnosis) is identified, cessation should be considered. Empiric studies have reported some limited success with use of tricyclic or SSRI-type antidepressants, as well as antiepileptic drugs such as carbamazepine, and low-dose zolpidem and benzodiazepines. A variety of interventional modalities may be brought to bear but in the majority of cases these should be done only under the direction of a specialist (Jackowich et al, 2016).

Female Orgasm Disorder

Female orgasm disorder is defined as persistent or recurrent compromise of orgasm frequency, intensity, timing, and/or pleasure (Parish et al, 2016). Like FGAD, it is important to note that the diagnosis of FOD should be restricted to those cases where a woman is receiving sexual stimulation that is of appropriate quantity and quality for her individual preferences; a woman who does not achieve orgasm because of the absence of preferred sexual stimulation would not meet the criteria. It is also important to note that many women who are sexually satisfied do not experience orgasm from vaginal penetration alone. There is a widespread cultural belief, derived in large part from >100-year-old theories of Sigmund Freud, that only orgasms experienced due to vaginal penetration are healthy (Freud, 1905). However, given the high prevalence of women who do not attain orgasm from vaginal penetration, and the absence of any clear abnormality in these women, there is no empiric support for this antique contention.

The prevalence of FOD is estimated at about 5% (Shifren et al, 2008). Difficulties with orgasm may stem in part from other sexual dysfunctions, relationship conflict/poor communication, and other psychosocial issues have been linked to difficulty in attaining orgasm (Dennerstein et al, 1999; Laumann et al, 1999). Antidepressants of the SSRI class are strongly associated with FOD (Rosen et al, 1999). There are no clear links between FOD and age, menopausal status, or race/ethnicity (Graham, 2010).

Management of FOD centers around addressing reversible causes (eg, SSRI medications) and enhancing communication between partners regarding sexual activity likely to trigger orgasm. These activities may be incorporated into sexual encounters (Shindel and Goldstein, 2016). Directed masturbation and self-exploration may help to identify triggers/activities for orgasm that are unique to a given woman (Heiman and Meston, 1997). Management of comorbid or precipitating sexual dysfunctions may also help to resolve issues with FOD (Shindel and Goldstein, 2016).

Sexual Pain Disorders

The problem of pain with sexual activity is a common one that may be a predisposing, precipitating, or comorbid sexual issue. Sexual pain may also be a standalone issue. The most commonly utilized term for this spectrum of conditions is **dyspareunia**, which is defined as genital pain that occurs before, during, or after sexual activity (Parish et al, 2016). Dyspareunia may be classified as superficial (hymen and vestibule), vaginal (introitus to cervix), or deep (supracervical). Dyspareunia is distinct from pain related to lack of vaginal lubrication and from spasm of the pelvic floor muscles near the vagina, leading to impossibility of vaginal penetration, a condition that is commonly referred to as **vaginismus**. Although this term is no longer preferred, it is still used in common parlance (Bornstein et al, 2016).

The lifetime prevalence of dyspareunia varies widely depending on population of interest and how the question is phrased, but a range of 7–32% has been reported (Laumann et al, 2005; Hayes et al, 2008). Pain with sexual activity appears to be most common in women at the extremes of age (younger and older) (Bancroft and Graham, 2011; Farage and Maibach, 2006; Landry and Bergeron, 2009). The etiology for this pain likely differs; vulvovaginal atrophy is likely to account for pain in older women, whereas inadequate sexual stimulation and/or pscyhorelational issues may be more relevant for young women. Specific medical conditions have also been associated with sexual pain. Superficial dyspareunia has been associated with neuroproliferative disorders of the vulvar vestibule, vulvar dermatoses, or anatomical variants (eg, persistent hymen, protuberant labia which may be tugged during intercourse) (Zolnoun et al, 2006; Bowen et al, 2008; Burrows et al, 2008). Deep dyspareunia has been associated with endometriosis, uterine leiomyoma, and/or ovarian cysts (Vercellini et al, 2012).

Pain is a neurocognitive phenomenon, and as such the relevance of cognitive and emotional factors cannot be overlooked. Mood and anxiety disorders are quite common in individuals with pain syndromes; these may lead to catastrophizing thoughts ("this pain will be unbearable") and/or loss of self-efficacy ("there is nothing I can do to make sex not hurt") (Desrochers et al, 2010). Women from conservative cultures may experience difficulty with sexual activity and are hence more prone to sexual pain (Yasan and Akdeniz, 2009). Sexual pain issues are also common in women who have been the victims of sexual violence (Nusbaum et al, 2005).

Attention to psychological factors is an important component in management of sexual pain syndromes (Rosenbaum and Owens, 2008; Bergeron et al, 2001). Care must be taken however to carefully assess and treat any physical issues that may contribute to pain as well. A thorough and meticulous examination of the external and internal genitalia is critical; this should include assessment of gynecological and urinary organs as well as musculoskeletal tone (Goldstein and Burrows, 2008). Failure to address both physical and mental components to sexual pain will lead to suboptimal outcomes.

Management of sexual pain disorders should be centered on resolving physical issues (eg, vulvovaginal atrophy, high pelvic floor muscle tone, vulvar dermatoses) using appropriate medical or physical therapy (Rosenbaum and Owens, 2008; North American Menopause Society, 2007; Salim and Wojnarowaksa, 2005). Specific examples include estrogens for vulvovaginal atrophy, topical agents for dermatoses, and pelvic floor physical therapy with or without the use of vaginal dilators for issues of pelvic muscle tone. Surgery may be indicated for some particular cases (Bergeron et al, 2001). Various forms of empiric medical therapy have been reported for sexual pain; evidence for these is generally sparse, but targeted therapy may be of benefit in some cases (Shindel and Goldstein, 2016). There is equivocal evidence to support the use of muscle relaxants (Bertolasi et al, 2009) or intravaginal benzodiazepines (Rogalski et al, 2010), but these should be utilized only in the setting of clear indications.

Ospemifine is a SERM that has estrogenic activity in bone and vaginal epithelium. The effects of ospemifene appear to be similar to those of topical estrogen in the vagina, with the theoretical benefit of selectivity for the bone and vaginal epithelium (Rutanen et al, 2003). Ospemifene has been approved by the FDA for the specific indication of dyspareunia in postmenopausal women (Portman et al, 2013). More recently, a dehydroepiandrosterone (DHEA) vaginal suppository has been approved by the FDA for management of dyspareunia from vulvovaginal atrophy (Labrie et al, 2016).

CONCLUSIONS

Sexuality is an important component of overall quality of life for women and their partners. Physicians can play an important role in optimizing women's sexual wellness by eliciting sexual health histories and offering education and treatment for sexual concerns. Appropriate referral and consultations will remain key. As additional evidence-based options become available for female sexual dysfunction, more physicians will be expected to take an active role in managing women's sexual concerns.

BIBLIOGRAPHY

Aaronson DS, Shindel AW: Advocating for safer use of sexual enhancement products. J Sex Med 2010;7(6):2285–2287.

Althof SE: What's new in sex therapy (CME). J Sex Med 2010;7(1 Pt 1): 5–13; quiz 14–15.

Altman D, Elmer C, Kiilholma P, et al: Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009;113(1):127–133.

Anderson D, Sievert LL, Melby MK, Obermeyer CM: Methods used in cross-cultural comparisons of sexual symptoms and their determinants. Maturitas 2011;70(2):135–140.

Antosh DD, Gutman RE: Diagnosis and management of female urethral diverticulum. Female Pelvic Med Reconstr Surg 2011; 17(6):264–271.

APA: Diagnostic and Statistical Manual of Mental Disorders. Vth ed. American Psychiatric Association, 2013.

Atis G, Dalkilinc A, Altuntas Y, Atis A, Caskurlu T, Ergenekon E: Sexual dysfunction in women with clinical hypothyroidism and subclinical hypothyroidism. J Sex Med 2010;7(7):2583–2590.

Bachmann G, Oza D: Female androgen insufficiency. Obstet Gynecol Clin North Am 2006;33(4):589–598.

Bachmann GA, Ebert GA, Burd ID: Vulvovaginal complaints. In: Lobo RA (ed): Treatment of the Postemonpausal Woman: Basic and Clinical Aspects. Lippincott Williams & Wilkins, Philadelphia, 1999, pp. 195–201.

Bancroft J, Graham CA: The varied nature of women's sexuality: Unresolved issues and a theoretical approach. Horm Behav 2011;59(5):717–729.

Bancroft J, Loftus J, Long JS: Distress about sex: A national survey of women in heterosexual relationships. Arch Sex Behav 2003; 32(3):193–208.

Basson R, McInnes R, Smith MD, Hodgson G, Koppiker N: Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. J Womens Health Gend Based Med 2002;11(4):367–377.

Basson R, Wierman ME, van Lankveld J, Brotto L: Summary of the recommendations on sexual dysfunctions in women. J Sex Med 2010;7(1 Pt 2):314–326.

Basson R: A model of women's sexual arousal. J Sex Marital Ther 2002;28(1):1–10.

Basson R: Rethinking low sexual desire in women. Br J Obstet Gynaecol 2002;109(4):357–363.

Bekker M, Beck J, Putter H, et al: The place of female sexual dysfunction in the urological practice: Results of a Dutch survey. J Sex Med 2009;6(11):2979–2987.

Bergeron S, Binik YM, Khalife S, et al: A randomized comparison of group cognitive–behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain 2001;91(3):297–306.

Bertolasi L, Frasson E, Cappelletti JY, Vicentini S, Bordignon M, Graziottin A: Botulinum neurotoxin type A injections for vaginismus secondary to vulvar vestibulitis syndrome. Obstet Gynecol 2009;114(5):1008–1016.

Bornstein J, Goldstein AT, Stockdale CK, et al: 2015 ISSVD, ISSWSH, and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia. J Sex Med 2016;13(4):607–612.

Bowen AR, Vester A, Marsden L, Florell SR, Sharp H, Summers P: The role of vulvar skin biopsy in the evaluation of chronic vulvar pain. Am J Obstet Gynecol 2008;199(5):467 e461–e466.

Brotto LA, Gorzalka BB: Genital and subjective sexual arousal in postmenopausal women: Influence of laboratory-induced hyperventilation. J Sex Marital Ther 2002;28(Suppl 1):39–53.

Brotto LA, Petkau AJ, Labrie F, Basson R: Predictors of sexual desire disorders in women. J Sex Med 2011;8(3):742–753.

Burger HG, Hale GE, Dennerstein L, Robertson DM: Cycle and hormone changes during perimenopause: The key role of ovarian function. Menopause 2008;15(4 Pt 1):603–612.

Burri A, Rahman Q, Santtila P, Jern P, Spector T, Sandnabba K: The relationship between same-sex sexual experience, sexual distress, and female sexual dysfunction. J Sex Med 2012;9(1):198–206.

Burrows LJ, Basha M, Goldstein AT: The effects of hormonal contraceptives on female sexuality: A review. J Sex Med 2012;9(9): 2213–2223.

Burrows LJ, Shaw HA, Goldstein AT: The vulvar dermatoses. J Sex Med 2008;5(2):276–283.

Caruso S, Rugolo S, Agnello C, Intelisano G, Di Mari L, Cianci A: Sildenafil improves sexual functioning in premenopausal women with type 1 diabetes who are affected by sexual arousal disorder: A double-blind, crossover, placebo-controlled pilot study. Fertil Steril 2006;85(5):1496–1501.

Chen J, Sweet G, Shindel A: Urinary disorders and female sexual function. Curr Urol Rep 2013;14(4):298–308.

Chivers ML, Seto MC, Lalumiere ML, Laan E, Grimbos T: Agreement of self-reported and genital measures of sexual arousal in men and women: A meta-analysis. Arch Sex Behav 2010;39(1):5–56.

Clayton AH, DeRogatis LR, Rosen RC, Pyke R: Intended or unintended consequences? The likely implications of raising the bar for sexual dysfunction diagnosis in the proposed DSM-V revisions: 1. For women with incomplete loss of desire or sexual receptivity. J Sex Med 2012;9(8):2027–2039.

Clayton AH, Montejo AL: Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiatry 2006;67(Suppl 6):33–37.

Clegg M, Towner A, Wylie K: Should questionnaires of female sexual dysfunction be used in routine clinical practice? Maturitas 2012;72(2):160–164.

Dasgupta R, Wiseman OJ, Kanabar G, Fowler CJ, Mikol D: Efficacy of sildenafil in the treatment of female sexual dysfunction due to multiple sclerosis. J Urol 2004;171(3):1189–1193; discussion 1193.

Davis SR, Worsley R, Miller KK, Parish SJ, Santoro N. Androgens and Female Sexual Function and Dysfunction-Findings From the Fourth International Consultation of Sexual Medicine. J Sex Med. 2016;13(2):168–178.

Davis SR, Wahlin-Jacobsen S. Testosterone in women-the clinical significance. Lancet Diabetes Endocrinol. 2015;3(12):980–992.

Davison SL, Bell RJ, LaChina M, Holden SL, Davis SR: The relationship between self-reported sexual satisfaction and general well-being in women. J Sex Med 2009;6(10):2690–2697.

Dennerstein L, Lehert P, Burger H, Dudley E: Factors affecting sexual functioning of women in the mid-life years. Climacteric 1999;2(4):254–262.

Desrochers G, Bergeron S, Khalife S, Dupuis MJ, Jodoin M: Provoked vestibulodynia: Psychological predictors of topical and cognitive-behavioral treatment outcome. Behav Res Ther 2010;48(2):106–115.

Diamant AL, Schuster MA, McGuigan K, Lever J: Lesbians' sexual history with men: Implications for taking a sexual history. Arch Intern Med 1999;159(22):2730–2736.

Donovan KA, Thompson LM, Hoffe SE: Sexual function in colorectal cancer survivors. Cancer Control 2010;17(1):44–51.

Elsamra S, Nazmy M, Shin D, Fisch H, Sawczuk I, Fromer D: Female sexual dysfunction in urological patients: Findings from a major metropolitan area in the USA. BJU Int 2010;106(4):524–526.

Esposito K, Giugliano F, Maiorino MI, Giugliano D: Dietary factors, Mediterranean diet and erectile dysfunction. J Sex Med 2010a; 7(7):2338–2345.

Esposito K, Maiorino MI, Bellastella G, Giugliano F, Romano M, Giugliano D: Determinants of female sexual dysfunction in type 2 diabetes. Int J Impot Res 2010b;22(3):179–184.

Farage M, Maibach H: Lifetime changes in the vulva and vagina. Arch Gynecol Obstet 2006;273(4):195–202.

FDA: Administration USFaD. ADDYI (flibanserin) tablets label. 2015.

Freud S. Drei Abhandlungen zur Sexualtheorie. Frankfurt am Main: Fischer; 1905.

Garvey LJ, West C, Latch N, Leiblum S, Goldmeier D: Report of spontaneous and persistent genital arousal in women attending a sexual health clinic. Int J STD AIDS 2009;20(8):519–521.

Gass ML, Cochrane BB, Larson JC, et al: Patterns and predictors of sexual activity among women in the Hormone Therapy trials of the Women's Health Initiative. Menopause 2011;18(11):1160–1171.

Gast MJ, Freedman MA, Vieweg AJ, et al: A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women. Menopause 2009;16(2):247–256.

Gelez H, Clement P, Compagnie S, et al: Brain neuronal activation induced by flibanserin treatment in female rats. Psychopharmacology (Berlin) 2013;230(4):639–652.

Giles KR, McCabe MP: Conceptualizing women's sexual function: Linear vs. circular models of sexual response. J Sex Med 2009; 6(10):2761–2771.

Giraldi A, Kristensen E: Sexual dysfunction in women with diabetes mellitus. J Sex Res 2010;47(2):199–211.

Goldberg DC, Whipple B, Fishkin RE, Waxman H, Fink PJ, Weisberg M: The Grafenberg spot and female ejaculation: A review of initial hypotheses. J Sex Marital Ther 1983;9(1):27–37.

Goldstein AT, Burrows L: Vulvodynia. J Sex Med 2008;5(1):5–14; quiz 15.

Goldstein I, Alexander JL: Practical aspects in the management of vaginal atrophy and sexual dysfunction in perimenopausal and postmenopausal women. J Sex Med 2005;2(Suppl 3):154–165.

Graham CA: The DSM diagnostic criteria for female orgasmic disorder. Arch Sex Behav 2010;39(2):256–270.

Greenspan S: A sex police for adults with "mental retardation"? Comment on Spiecker and Steutel. J Moral Educ 2002;31(2): 171–179.

Greer WJ, Richter HE, Wheeler TL, et al: Long-term outcomes of the Total or Supracervical Hysterectomy (TOSH) trial. Female Pelvic Med Reconstr Surg 2010;16(1):49–57.

Harte CB, Meston CM: Acute effects of nicotine on physiological and subjective sexual arousal in nonsmoking men: A randomized, double-blind, placebo-controlled trial. J Sex Med 2008;5(1):110–121.

Hatzichristou D, Kirana PS, Banner L, et al: Diagnosing sexual dysfunction in men and women: Sexual history taking and the role of symptom scales and questionnaires. J Sex Med 2016;13(8):1166–1182.

Hayes RD, Dennerstein L, Bennett CM, Fairley CK: What is the "true" prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? J Sex Med 2008;5(4):777–787.

Heiman JR, Meston CM: Evaluating sexual dysfunction in women. Clin Obstet Gynecol 1997;40(3):616–629.

Herbenick D, Reece M, Hensel D, Sanders S, Jozkowski K, Fortenberry JD: Association of lubricant use with women's sexual pleasure, sexual satisfaction, and genital symptoms: A prospective daily diary study. J Sex Med 2011;8(1):202–212.

Herbenick D, Reece M, Sanders SA, Dodge B, Ghassemi A, Fortenberry JD: Women's vibrator use in sexual partnerships: Results from a nationally representative survey in the United States. J Sex Marital Ther 2010;36(1):49–65.

Herbenick D, Schick V, Reece M, Sanders S, Dodge B, Fortenberry JD: The Female Genital Self-Image Scale (FGSIS): Results from a nationally representative probability sample of women in the United States. J Sex Med 2011;8(1):158–166.

Hodgins MB, Spike RC, Mackie RM, MacLean AB: An immunohistochemical study of androgen, oestrogen and progesterone receptors in the vulva and vagina. Br J Obstet Gynaecol 1998;105(2):216–222.

Incrocci L, Jensen PT: Pelvic radiotherapy and sexual function in men and women. J Sex Med 2013;10 (Suppl 1):53–64.

Jackowich RA, Pink L, Gordon A, Pukall CF: Persistent genital arousal disorder: A review of its conceptualizations, potential origins, impact, and treatment. Sex Med Rev 2016;4(4):329–342.

Kaplan H: The New Sex Therapy. Brunner/Mazel, New York, 1977.

Katz M, DeRogatis LR, Ackerman R, et al: Efficacy of flibanserin in women with hypoactive sexual desire disorder: Results from the BEGONIA trial. J Sex Med 2013;10(7):1807–1815.

Kennedy C: Functioning and disability associated with mental disorders: The evolution since ICIDH. Disabil Rehabil 2003; 25(11–12):611–619.

Kingsberg S, Althof SE: Evaluation and treatment of female sexual disorders. Int Urogynecol J Pelvic Floor Dysfunct 2009;20(Suppl 1): S33–S43.

Labrie F, Archer DF, Koltun W, et al: Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause 2016;23(3):243–256.

Landen M, Eriksson E, Agren H, Fahlen T: Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. J Clin Psychopharmacol 1999; 19(3):268–271.

Landry T, Bergeron S: How young does vulvo-vaginal pain begin? Prevalence and characteristics of dyspareunia in adolescents. J Sex Med 2009;6(4):927–935.

Laumann EO, Nicolosi A, Glasser DB, et al: Sexual problems among women and men aged 40-80 y: Prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res 2005;17(1):39–57.

Laumann EO, Paik A, Rosen RC: Sexual dysfunction in the United States: Prevalence and predictors. JAMA 1999;281(6):537–544.

Leeman LM, Rogers RG: Sex after childbirth: Postpartum sexual function. Obstet Gynecol 2012;119(3):647–655.

Leiblum S, Seehuus M, Brown C: Persistent genital arousal: Disordered or normative aspect of female sexual response? J Sex Med 2007; 4(3):680–687; discussion 687–689.

Liao Q, Zhang M, Geng L, et al: Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: A double-blind, placebo-controlled study in Chinese population. J Sex Med 2008;5(8):1923–1931.

Lloyd J, Crouch NS, Minto CL, Liao LM, Creighton SM: Female genital appearance: "Normality" unfolds. Br J Obstet Gynaecol 2005;112(5):643–646.

Makadon HJ: Ending LGBT invisibility in health care: The first step in ensuring equitable care. Cleve Clin J Med 2011;78(4):220–224.

Martin-Alguacil N, Schober J, Kow LM, Pfaff D: Arousing properties of the vulvar epithelium. J Urol 2006;176(2):456–462.

Masters WH, Johnson VE: Human Sexual Response. Springer, New York, 1966.

Mazloomdoost D, Pauls RN: A comprehensive review of the clitoris and its role in female sexual function. Sex Med Rev 2015;3(4):245–263.

McCabe M, Althof SE, Assalian P, et al: Psychological and interpersonal dimensions of sexual function and dysfunction. J Sex Med 2010;7(1 Pt 2):327–336.

Millheiser L: Female sexual function during pregnancy and postpartum. J Sex Med 2012;9(2):635–636.

Moynihan R: Drug maker urges group to lobby FDA on testosterone for women. BMJ 2004;329(7477):1255.

Munarriz R, Kim NN, Goldstein I, Traish AM: Biology of female sexual function. Urol Clin North Am 2002;29(3):685–693.

Musicki B, Liu T, Lagoda GA, Bivalacqua TJ, Strong TD, Burnett AL: Endothelial nitric oxide synthase regulation in female genital tract structures. J Sex Med 2009;6(Suppl 3):247–253.

Nicolosi A, Laumann EO, Glasser DB, Brock G, King R, Gingell C: Sexual activity, sexual disorders and associated help-seeking behavior among mature adults in five Anglophone countries from the Global Survey of Sexual Attitudes and Behaviors (GSSAB). J Sex Marital Ther 2006;32(4):331–342.

North American Menopause Society: The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause 2007;14(3 Pt 1):355–369; quiz 370–351.

Nusbaum MM, Braxton L, Strayhorn G: The sexual concerns of African American, Asian American, and white women seeking routine gynecological care. J Am Board Fam Pract 2005;18(3): 173–179.

O'Connell HE, Eizenberg N, Rahman M, Cleeve J: The anatomy of the distal vagina: towards unity. J Sex Med 2008;5(8): 1883–1891.

Parish SJ, Goldstein AT, Goldstein SW, et al: Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions-Part II. J Sex Med 2016.

Park K, Han HJ, Kim SW, et al: Expression of aquaporin water channels in rat vagina: Potential role in vaginal lubrication. J Sex Med 2008;5(1):77–82.

Pauleta JR, Pereira NM, Graca LM: Sexuality during pregnancy. J Sex Med 2010;7(1 Pt 1):136–142.

Pauls RN, Occhino JA, Dryfhout VL: Effects of pregnancy on female sexual function and body image: A prospective study. J Sex Med 2008;5(8):1915–1922.

Portman DJ, Bachmann GA, Simon JA: Ospemifene Study G. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause 2013;20(6):623–630.

Raina R, Pahlajani G, Khan S, Gupta S, Agarwal A, Zippe CD: Female sexual dysfunction: Classification, pathophysiology, and management. Fertil Steril 2007;88(5):1273–1284.

Rogalski MJ, Kellogg-Spadt S, Hoffmann AR, Fariello JY, Whitmore KE: Retrospective chart review of vaginal diazepam suppository use in high-tone pelvic floor dysfunction. Int Urogynecol J 2010;21(7):895–899.

Roovers JP, van der Bom A, van Leeuwen JS, Scholten P, Heintz P, van der Vaart H: Effects of genital prolapse surgery on sexuality. J Psychosom Obstet Gynaecol 2006;27(1):43–48.

Roovers JP, van der Bom JG, van der Vaart CH, Heintz AP: Hysterectomy and sexual wellbeing: Prospective observational study of vaginal hysterectomy, subtotal abdominal hysterectomy, and total abdominal hysterectomy. BMJ 2003;327(7418):774–778.

Rosen RC, Lane RM, Menza M: Effects of SSRIs on sexual function: A critical review. J Clin Psychopharmacol 1999;19(1):67–85.

Rosenbaum TY, Owens A: The role of pelvic floor physical therapy in the treatment of pelvic and genital pain-related sexual dysfunction (CME). J Sex Med 2008;5(3):513–523; quiz 524–515.

Rossouw JE, Manson JE, Kaunitz AM, Anderson GL: Lessons learned from the Women's Health Initiative trials of menopausal hormone therapy. Obstet Gynecol 2013;121(1):172–176.

Rowen TS, Stein S, Tepper M: Sexual health care for people with physical disabilities. J Sex Med 2015;12(3):584–589.

Rutanen EM, Heikkinen J, Halonen K, Komi J, Lammintausta R, Ylikorkala O: Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: A double-blind, randomized trial. Menopause 2003;10(5):433–439.

Sadovsky R, Nusbaum M: Sexual health inquiry and support is a primary care priority. J Sex Med 2006;3(1):3–11

Salim A, Wojnarowaksa F: Skin diseases affecting the vulva. Curr Obest Gynecol 2005;15:97–107.

Sand M, Fisher WA: Women's endorsement of models of female sexual response: The nurses' sexuality study. J Sex Med 2007;4(3): 708–719.

Sarrel PM: Effects of hormone replacement therapy on sexual psychophysiology and behavior in postmenopause. J Womens Health Gend Based Med 2000;9(Suppl 1):S25–S32.

Schick V, Rosenberger JG, Herbenick D, Reece M: Sexual behaviour and risk reduction strategies among a multinational sample of women who have sex with women. Sex Transm Infect 2012; 88(6):407–412.

Schober JM, Pfaff D: The neurophysiology of sexual arousal. Best Pract Res Clin Endocrinol Metab 2007;21(3):445–461.

Schulte-Herbruggen O, Ahlers CJ, Kronsbein JM, et al: Impaired sexual function in patients with borderline personality disorder is determined by history of sexual abuse. J Sex Med 2009;6(12):3356–3363.

Shifren JL, Davis SR, Moreau M, et al: Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause 2006;13(5):770–779.

Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB: Sexual problems and distress in United States women: Prevalence and correlates. Obstet Gynecol 2008;112(5):970–978.

Shindel AW, Goldstein I: Sexual function and dysfunction in the female. In: Wein A (ed): Campbell-Walsh Urology. 11th ed. Elsevier, 2016, pp. 749–-764.

Shindel AW, Rowen TS, Lin TC, Li CS, Robertson PA, Breyer BN: An Internet survey of demographic and health factors associated with risk of sexual dysfunction in women who have sex with women. J Sex Med 2012;9(5):1261–1271.

Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M Jr., Sand M: Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: Results of the SNOWDROP trial. Menopause. 2014;21(6):633-640.

Sipski ML, Rosen RC, Alexander CJ, Hamer RM: Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. Urology 2000;55(6):812–815.

Sobecki JN, Curlin FA, Rasinski KA, Lindau ST: What we don't talk about when we don't talk about sex: Results of a national survey of U.S. obstetrician/gynecologists. J Sex Med 2012;9(5):1285–1294.

Spiecker B, Steutel J: Sex between people with "mental retardation": An ethical evaluation. J Moral Educ 2002;31(2):155–169.

Stevens DM, Weems JM, Brown L, Barbour KA, Stahl SM. The pharmacodynamic effects of combined administration of flibanserin and alcohol. J Clin Pharm Ther. 2017;42(5):598–606.

Stott DB: The training needs of general practitioners in the exploration of sexual health matters and providing sexual healthcare to lesbian, gay and bisexual patients. Med Teach 2013;35(9): 752–759.

Suh DD, Yang CC, Cao Y, Garland PA, Maravilla KR: Magnetic resonance imaging anatomy of the female genitalia in premenopausal and postmenopausal women. J Urol 2003;170(1):138–144.

Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K: Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev 2013(5):CD003382.

Taylor R: A Practical Treatise on Sexual Disorders of the Male and Female. Lea Brothers, New York, 1897.

Thorp J, Simon J, Dattani D, et al: Treatment of hypoactive sexual desire disorder in premenopausal women: Efficacy of flibanserin in the DAISY study. J Sex Med 2012;9(3):793–804.

Tiefer L: Beneath the veneer: The troubled past and future of sexual medicine. J Sex Marital Ther 2007;33(5):473–477.

Tiefer L: Sexual behaviour and its medicalisation. Many (especially economic) forces promote medicalisation. BMJ 2002;325 (7354):45.

Traish AM, Botchevar E, Kim NN: Biochemical factors modulating female genital sexual arousal physiology. J Sex Med 2010;7(9):2925–2946.

Vercellini P, Somigliana E, Buggio L, Barbara G, Frattaruolo MP, Fedele L: "I can't get no satisfaction": Deep dyspareunia and sexual functioning in women with rectovaginal endometriosis. Fertil Steril 2012;98(6):1503–-1511, e1501.

Waite LJ, Laumann EO, Das A, Schumm LP: Sexuality: measures of partnerships, practices, attitudes, and problems in the National Social Life, Health, and Aging Study. J Gerontol B Psychol Sci Soc Sci 2009;64(Suppl 1):56–66.

Waldinger MD, Schweitzer DH: Persistent genital arousal disorder in 18 Dutch women: Part II. A syndrome clustered with restless legs and overactive bladder. J Sex Med 2009;6(2):482–497.

Wallen K, Lloyd EA: Female sexual arousal: Genital anatomy and orgasm in intercourse. Horm Behav 2011;59(5):780–792.

Wehbe SA, Kellogg S, Whitmore K: Urogenital complaints and female sexual dysfunction. Part 2. J Sex Med 2010;7(7): 2304–2317; quiz 2318–2309.

WHO: Defining Sexual Health. World Health Organization, Geneva, 2006.

WHO: Global and Regional Estimtes of Violence against Women. World Health Organization, Geneva, 2013.

Wierman ME, Nappi RE, Avis N, et al: Endocrine aspects of women's sexual function. J Sex Med 2010;7(1 Pt 2):561–585.

Witting K, Santtila P, Varjonen M, et al: Female sexual dysfunction, sexual distress, and compatibility with partner. J Sex Med 2008;5(11):2587–2599.

Woodard TL, Diamond MP: Physiologic measures of sexual function in women: A review. Fertil Steril 2009;92(1):19-34.

Xu F, Sternberg MR, Markowitz LE: Women who have sex with women in the United States: prevalence, sexual behavior and prevalence of herpes simplex virus type 2 infection-results from national health and nutrition examination survey 2001-2006. Sex Transm Dis 2010;37(7):407–413

Yang CC, Cold CJ, Yilmaz U, Maravilla KR: Sexually responsive vascular tissue of the vulva. BJU Int 2006;97(4):766–772.

Yasan A, Akdeniz N: Treatment of lifelong vaginismus in traditional Islamic couples: A prospective study. J Sex Med 2009;6(4):1054–1061.

Yucel S, Baskin LS: An anatomical description of the male and female urethral sphincter complex. J Urol 2004;171(5):1890–1897.

Zippe CD, Raina R, Shah AD, et al: Female sexual dysfunction after radical cystectomy: A new outcome measure. Urology 2004;63(6): 1153–1157.

Zolnoun D, Hartmann K, Lamvu G, As-Sanie S, Maixner W, Steege J: A conceptual model for the pathophysiology of vulvar vestibulitis syndrome. Obstet Gynecol Surv 2006;61(6):395–401; quiz 423.

Disorders of the Penis and Male Urethra

41

Benjamin N. Breyer, MD, MAS, FACS; &
Jack W. McAninch, MD, FACS, FRCS(E)(Hon)

CONGENITAL ANOMALIES OF THE PENIS

APENIA

Congenital absence of the penis (apenia) is extremely rare. In this condition, the urethra generally opens on the perineum or inside the rectum. The child should undergo a karyotype and referral to a disorders of sexual differentiation (DSD) specialist.

MEGALOPENIS

Megalopenis is characterized by rapid enlargement of the penis during childhood in boys with abnormalities that increase the production of testosterone. Examples of these abnormalities are interstitial cell tumors of the testicle, hyperplasia, or tumors of the adrenal cortex. Management is by correction of the underlying endocrine problem.

MICROPENIS

Micropenis is a more common anomaly and has been attributed to a testosterone deficiency that results in poor growth of organs that are targets of this hormone. A penis smaller than 2SD (standard deviations) from the norm is considered a micropenis (see Table 41–1). The testicles are small and frequently undescended. Other organs, including the scrotum, may be involved. Early evidence suggests that the ability of the hypothalamus to secrete luteinizing hormone-releasing hormone (LHRH) is decreased. The pituitary–gonadal axis appears to be intact, since the organs respond to testosterone, although this response may be sluggish at times. Studies have shown that topical application of 5% testosterone cream causes increased penile growth, but its effect is due to absorption of the hormone, which systemically stimulates genital growth. Patients with micropenis must be carefully evaluated for other endocrine and central nervous system (CNS) anomalies. Retarded bone growth, anosmia, learning disabilities, and deficiencies of adrenocorticotropic hormone and thyrotropin have been associated with micropenis. In addition, the possibility of DSD problems must be carefully investigated before therapy is begun.

The approach to management of micropenis has undergone gradual change in recent years, but androgen replacement is the basic requirement. The objective is to provide sufficient testosterone to stimulate penile growth without altering growth and closure of the epiphyses. A regimen of 25 mg orally every 3 weeks for no more than four doses has been recommended. Penile growth is assessed by measuring the length of the stretched penis (pubis to glans) before and after treatment. Therapy should begin by age 1 year and aim at maintaining genital growth commensurate with general body growth. Repeat courses of therapy may be required if the size of the penis falls behind as the child grows. For undescended testicles, orchiopexy should be done before the child is 2 years old. In the future, treatment with LHRH may correct micropenis as well as cause descent of the testicles, but at present, LHRH is not approved for such use.

ADULT PENILE SIZE

In recent years, penile augmentation and enhancement procedures have been done with increasing frequency, although no validation of success has been documented. Suspensory ligament release with pubic fat pad advancement, fat injections, and dermal fat grafts have been used in attempts to enhance penile size. Many consider that these procedures have not been proved safe or efficacious in normal men. Wessells et al (1996) evaluated penile size in the flaccid and erect states in otherwise normal adult men and found very good correlation between stretched and erect lengths (R^2 = .793; Table 41–2). This information can provide a guideline for physicians whose patients are concerned with their penile dimensions.

Table 41–1. Size of unstretched penis and testis from infancy to adulthood.

Age (years)	Length of penis (cm ± SD)	Diameter of testis (cm ± SD)
0.2–2	2.7 ± 0.5	1.4 ± 0.4
2.1–4	3.3 ± 0.4	1.2 ± 0.4
4.1–6	3.9 ± 0.9	1.5 ± 0.6
6.1–8	4.2 ± 0.8	1.8 ± 0.3
8.1–10	4.9 ± 1	2 ± 0.5
10.1–12	5.2 ± 1.3	2.7 ± 0.7
12.1–14	6.2 ± 2	3.4 ± 0.8
14.1–16	8.6 ± 2.4	4.1 ± 1
16.1–18	9.9 ± 1.7	5 ± 0.5
18.1–20	11 ± 1.1	5 ± 0.3
20.1–25	12.4 ± 1.6	5.2 ± 0.6

Data from Winter JS, Faiman C: Pituitary-gonadal relations in male children and adolescents. Pediatr Res. 1972 Feb;6(2):126–135.

CONGENITAL ANOMALIES OF THE URETHRA

DUPLICATION OF THE URETHRA

Duplication of the urethra is rare. The structures may be complete or incomplete. Resection of all but one complete urethra is recommended.

URETHRAL STRICTURE

Congenital urethral stricture is uncommon in infant boys. The fossa navicularis and membranous urethra are the two most common sites. Severe strictures may cause bladder damage and hydronephrosis (see Chapter 12), with symptoms of obstruction (urinary frequency and urgency) or urinary infection. A careful history and physical examination are indicated in patients with these complaints. Excretory urography and excretory voiding urethrography often define the lesion and the extent of obstruction. Retrograde urethrography (Figure 41–1) may also be helpful. Cystoscopy and urethroscopy should be performed in all patients in whom urethral stricture is suspected.

Table 41–2. Adult penile size: relationships among flaccid, stretched, and erect measurements.[a]

Penile state	Length (cm)	Circumference (cm)
Flaccid	8.8	9.7
Stretched	12.4	—
Erect	12.9	12.3

[a] Data represent the mean of measurements in 80 men and compiled from Wessels H, Lue TF, McAninch JW: Penile length in the flaccid and erect states: Guidelines for penile augmentation. J Urol. 1996 Sep; 156(3):995–997.

Strictures can be treated at the time of endoscopy. Diaphragmatic strictures may respond to dilation or visual urethrotomy. Other strictures should be treated under direct vision by internal urethrotomy with the currently available pediatric urethrotome. It may be necessary to repeat these procedures in order to stabilize the stricture. Single-stage open surgical repair by anastomotic urethroplasty, buccal mucosa graft, or penile flap is desirable if the obstruction recurs.

POSTERIOR URETHRAL VALVES

Posterior urethral valves, the most common obstructive urethral lesions in infants and newborns, occur only in males and are found at the distal prostatic urethra. The valves are mucosal folds that resemble thin membranes; they may cause varying degrees of obstruction when the child attempts to void (Figure 41–2).

▶ Clinical Findings

A. Symptoms and Signs

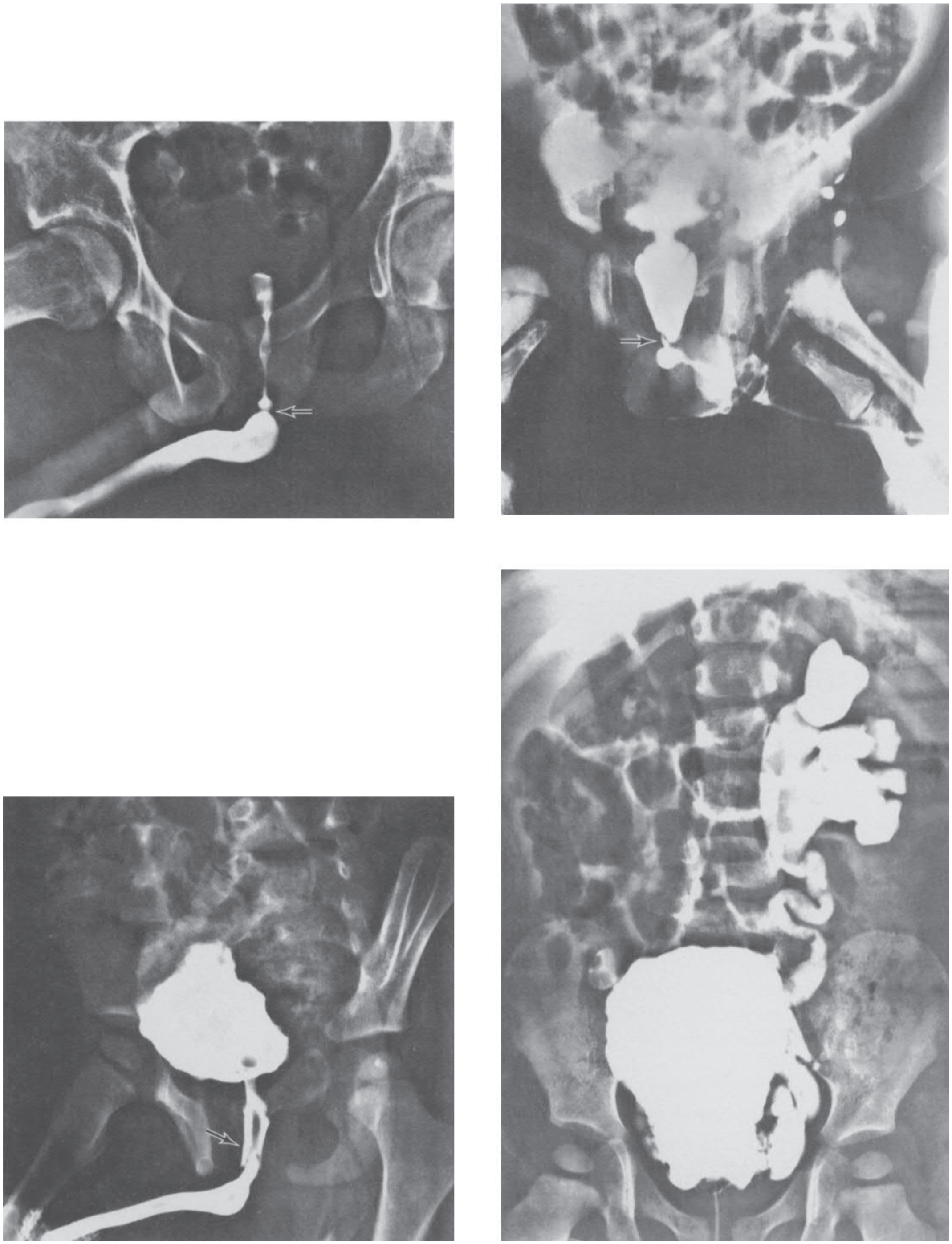
Children with posterior urethral valves may present with mild, moderate, or severe symptoms of obstruction. They often have a poor, intermittent, dribbling urinary stream. Urinary infection and sepsis occur frequently. Severe obstruction may cause hydronephrosis (see Chapter 11), which is apparent as a palpable abdominal mass. A palpable midline mass in the lower abdomen is typical of a distended bladder. Occasionally, palpable flank masses indicate hydronephrotic kidneys. In many patients, failure to thrive may be the only significant symptom, and examination may reveal nothing more than evidence of chronic illness.

B. Laboratory Findings

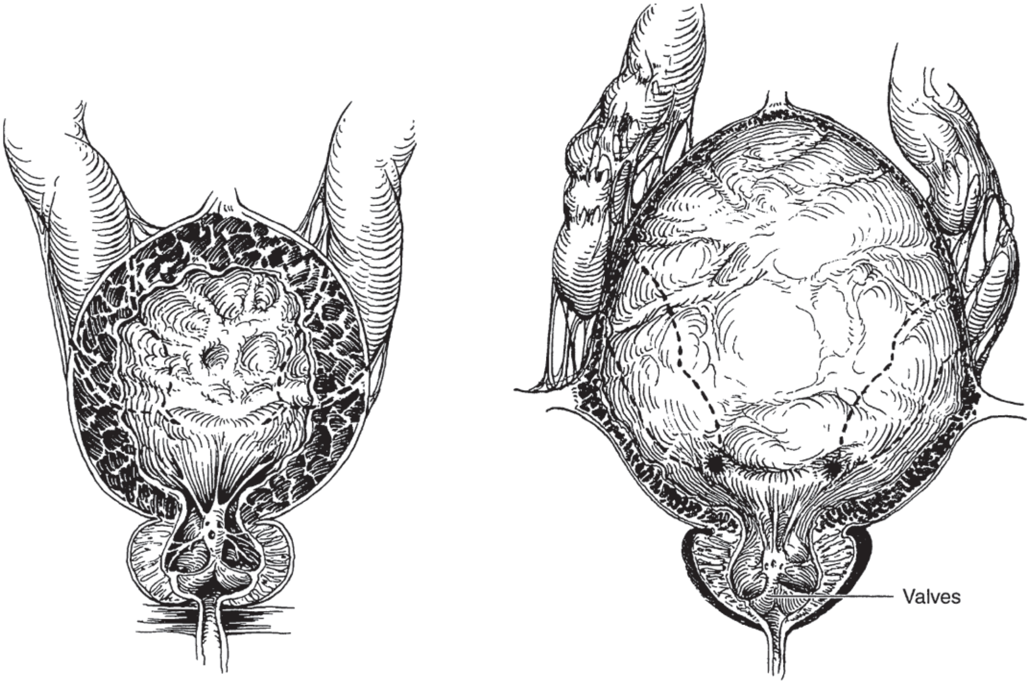
Azotemia and poor concentrating ability of the kidney are common findings. The urine is often infected, and anemia may be found if infection is chronic. Serum creatinine and blood urea nitrogen levels and creatinine clearance are the best indicators of the extent of renal failure.

C. X-Ray Findings

Voiding cystourethrography is the best radiographic study available to establish the diagnosis of posterior urethral valves. The presence of large amounts of residual urine is apparent on initial catheterization performed in conjunction with radiographic studies, and an uncontaminated urine



▲ **Figure 41–1.** ***Upper left:*** Retrograde urethrogram showing congenital diaphragmatic stricture. ***Upper right:*** Posterior urethral valves revealed on voiding cystourethrography. *Arrow* points to area of severe stenosis at distal end of prostatic urethra. ***Lower left:*** Posterior urethral valves. Patient would not void with cystography. Retrograde urethrogram showing valves (*arrow*). ***Lower right:*** Cystogram, same patient. Free vesicoureteral reflux and vesical trabeculation with diverticula.



▲ **Figure 41–2.** Posterior urethral valves. ***Left:*** Dilatation of the prostatic urethra, hypertrophy of vesical wall and trigone in stage of compensation; bilateral hydroureters secondary to trigonal hypertrophy. ***Right:*** Attenuation of bladder musculature in stage of decompensation; advanced ureteral dilatation and tortuosity, usually secondary to vesicoureteral reflux.

specimen should be obtained via the catheter and sent for culture. The cystogram may show vesicoureteral reflux and the severe trabeculations of longstanding obstruction, and the voiding cystourethrogram often demonstrates elongation and dilatation of the posterior urethra, with a prominent bladder neck (Figure 41–1). Excretory urograms may reveal hydroureter and hydronephrosis when obstruction is severe and longstanding.

D. Ultrasonography

Ultrasonography can be used to detect hydronephrosis, hydroureter, and bladder distention in children with severe azotemia. It can also detect fetal hydronephrosis, which is typical of urethral valves, as early as 28 weeks of gestation; when the obstruction is from valves, an enlarged bladder with bilateral hydroureteronephrosis is usually present.

E. Instrumental Examination

Urethroscopy and cystoscopy, performed with the patient under general anesthesia, show vesical trabeculation and cellules and, occasionally, vesical diverticula. The bladder neck and trigone may be hypertrophied. The diagnosis is confirmed by visual identification of the valves at the distal prostatic urethra. Supravesical compression shows that the valves cause obstruction.

▶ Treatment

Treatment consists of destruction of the valves, but the approach depends on the degree of obstruction and the general health of the child. In children with mild to moderate obstruction and minimal azotemia, transurethral fulguration of the valves is usually successful. Occasionally, catheterization, cystoscopy, or urethral dilation by perineal urethrostomy destroys the valves.

The more severe degrees of obstruction create varying grades of hydronephrosis requiring individualized management. Treatment of children with urosepsis and azotemia associated with hydronephrosis includes use of antibiotics, catheter drainage of the bladder, and correction of the fluid and electrolyte imbalance. Vesicostomy may be of benefit in patients with reflux and renal dysplasia.

In the most severe cases of hydronephrosis, vesicostomy or removal of the valves may not be sufficient because of ureteral atony, obstruction of the ureterovesical junction from trigonal hypertrophy, or both. In such cases, percutaneous loop ureterostomies may be done to preserve renal function and allow resolution of the hydronephrosis. After renal function is stabilized, valve ablation and reconstruction of the urinary tract can be done.

The period of proximal diversion should be as short as possible, since vesical contracture can be permanent after prolonged supravesical diversion.

It has been noted that approximately 50% of children with urethral valves have vesicoureteral reflux and that the prognosis is worse if the reflux is bilateral. After removal of the obstruction, reflux ceases spontaneously in about one-third of patients. In the remaining two-thirds of patients, the reflux should be corrected surgically.

Prognosis

Early detection is the best way to preserve kidney and bladder function. This can be accomplished by ultrasonography in utero, by careful physical examination and observation of voiding in the newborn, and by thorough evaluation of children who have urinary tract infections. Children in whom azotemia and infection persist after relief of obstruction have a poor prognosis.

ANTERIOR URETHRAL VALVES

Signs of anterior urethral valves, a rare congenital anomaly, are urethral dilatation or diverticula proximal to the valve, bladder outlet obstruction, postvoiding incontinence, and infection. Enuresis may be present. Urethroscopy and voiding cystourethrography will demonstrate the lesion, and endoscopic electrofulguration will effectively correct the obstruction.

URETHRORECTAL AND VESICORECTAL FISTULAS

Urethrorectal and vesicorectal fistulas are rare and are almost always associated with imperforate anus. Failure of the urorectal septum to develop completely and separate the rectum from the urogenital tract permits communication between the two systems (see Chapter 2). The child with such a fistula passes fecal material and gas through the urethra. If the anus has developed normally (ie, if it opens externally), urine may pass through the rectum.

Cystoscopy and panendoscopy usually show the fistulous opening. Radiographic contrast material given by mouth will reach the blind rectal pouch, and the distance between the end of the rectum and the perineum can be seen on appropriate radiograms.

Imperforate anus must be opened immediately and the fistula closed, or if the rectum lies quite high, temporary sigmoid colostomy should be performed. Definitive surgery, with repair of the urethral fistula, can be done later.

HYPOSPADIAS

In hypospadias, the urethral meatus opens on the ventral side of the penis proximal to the tip of the glans penis (Figure 41–3).

Sexual differentiation and urethral development begin in utero at approximately 8 weeks and are complete by 15 weeks. The urethra is formed by the fusion of the urethral folds along the ventral surface of the penis, which extends to the corona on the distal shaft. The glandular urethra is formed by canalization of an ectodermal cord that has grown through the glans to communicate with the fused urethral folds (see Chapter 2). Hypospadias results when fusion of the urethral folds is incomplete.

Hypospadias occurs in 1 in every 300 male children. Estrogens and progestins given during pregnancy are known to increase the incidence. Although a familial pattern of hypospadias has been recognized, no specific genetic traits have been established.

Classification

There are several forms of hypospadias classified according to location: (1) glandular, that is, opening on the proximal glans penis; (2) coronal, that is, opening at the coronal sulcus; (3) penile shaft; (4) penoscrotal; and (5) perineal. About 70% of all cases of hypospadias are distal penile or coronal.

Hypospadias in the male is evidence of feminization. Patients with penoscrotal and perineal openings should be considered to have potential DSD problems requiring appropriate evaluation. Hypospadiac newborns should not be circumcised, because the preputial skin may be useful for future reconstruction.

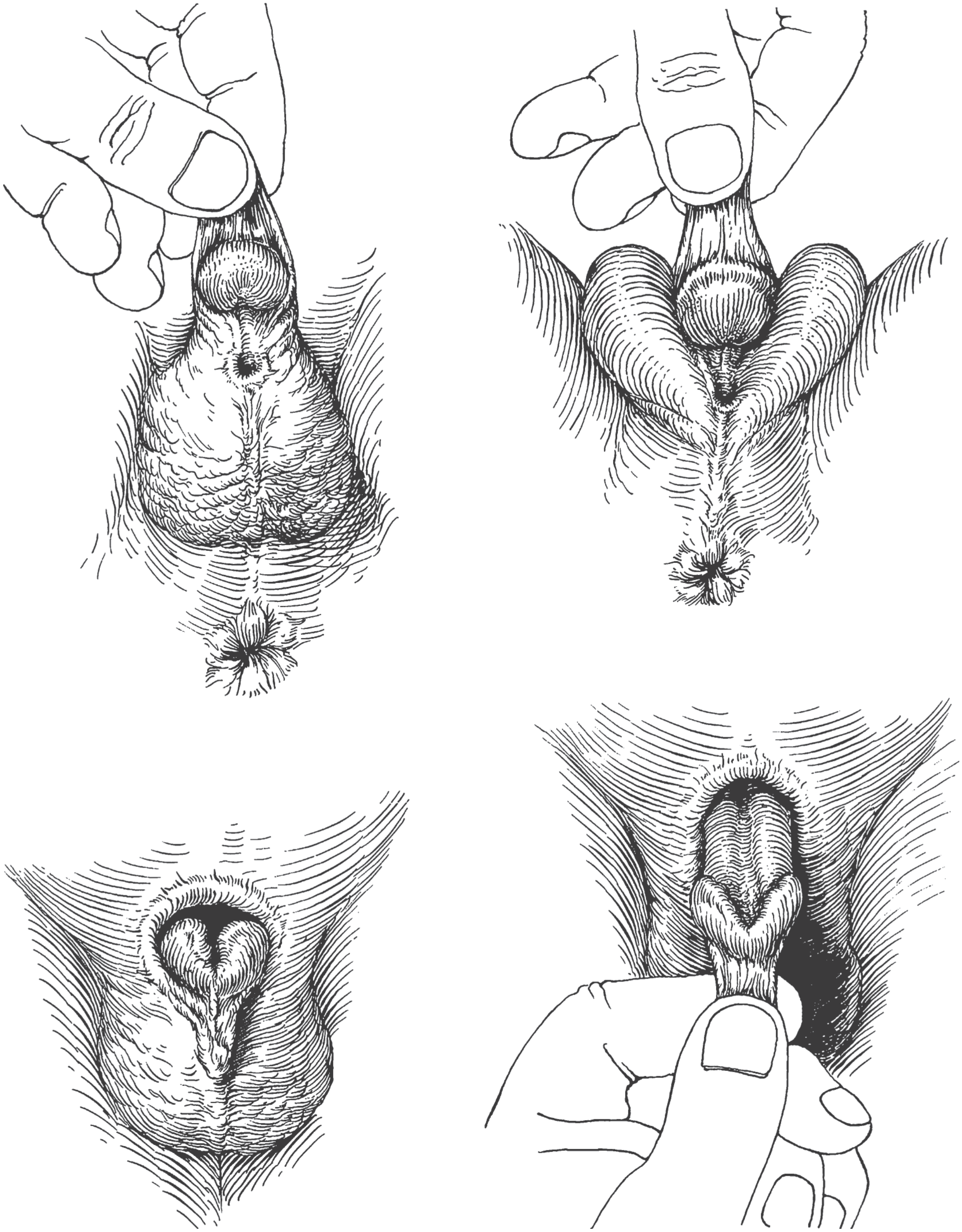
Clinical Findings

A. Symptoms and Signs

Although newborns and young children seldom have symptoms related to hypospadias, older children and adults may complain of difficulty directing the urinary stream and stream spraying. Chordee (curvature of the penis) causes ventral bending and bowing of the penile shaft, which can prevent sexual intercourse. Perineal or penoscrotal hypospadias necessitates voiding in the sitting position, and these proximal forms of hypospadias in adults can be the cause of infertility. An additional complaint of almost all patients is the abnormal (hooded) appearance of the penis, caused by deficient or absent ventral foreskin. The hypospadias meatus may be stenotic and should be carefully examined and calibrated. (A meatotomy should be done when stenosis exists.) There is an increased incidence of undescended testicles in children with hypospadias; scrotal examination is necessary to establish the position of the testicles.

B. Laboratory, X-Ray, and Endoscopic Findings

Since children with penoscrotal and perineal hypospadias often have a bifid scrotum and ambiguous genitalia, a buccal smear and karyotyping are indicated to help establish the genetic sex. Urethroscopy and cystoscopy are of value to determine whether internal male sexual organs are normally



▲ **Figure 41–3.** Hypospadias and epispadias. ***Upper left:*** Hypospadias, penoscrotal type. Redundant dorsal foreskin that is deficient ventrally; ventral chordee. ***Upper right:*** Hypospadias, midscrotal type. Chordee more marked. Penis often small. ***Lower left:*** Epispadias. Redundant ventral foreskin that is absent dorsally; severe dorsal chordee. ***Lower right:*** Traction on foreskin reveals dorsal defect.

developed. Excretory urography is also indicated in these patients to detect additional congenital anomalies of the kidneys and ureters.

Some authors recommend routine use of excretory urography for all patients with hypospadias; however, this seems to be of little value in the more distal types of the disorder, because there appears to be no increased incidence of upper urinary tract anomalies.

Differential Diagnosis

Any degree of hypospadias is an expression of feminization. Perineal and scrotal urethral openings should be carefully evaluated to ascertain that the patient is not a female with androgenized adrenogenital syndrome. Urethroscopy and cystoscopy will aid in evaluating the development of internal reproductive organs.

Treatment

For psychological reasons, hypospadias should be repaired before the patient reaches school age; in most cases, this can be done before age 2.

More than 150 methods of corrective surgery for hypospadias have been described. Currently, one-stage repairs with foreskin island flaps and incised urethral plate are performed by many urologists. It now appears that buccal mucosa grafts are more advantageous than others and should be considered the primary grafting technique when indicated. Fistulas occur in 15–30% of patients, but the fistula repair is considered a small, second-stage reconstruction.

All types of repair involve straightening the penis by removal of the chordee. The chordee removal can be confirmed by producing an artificial erection in the operating room following urethral reconstruction and advancement. Most successful techniques for repair of hypospadias use local skin and foreskin in developing the neourethra. In recent years, advancement of the urethra to the glans penis has become technically feasible and cosmetically acceptable.

Prognosis

After corrective surgery, most patients are able to void in the standing position as well as to deposit semen into the vagina. The overall cosmetic appearance and the prevention of fistula formation remain the greatest challenges in these repairs.

CHORDEE WITHOUT HYPOSPADIAS

Congenital ventral chordee without hypospadias is seen occasionally and is caused by a short urethra, fibrous tissues surrounding the corpus spongiosum, or both. The urethral opening is in the normal position on the glans penis; only with erection does the penis bow, thus preventing satisfactory vaginal penetration. During examination, if the patient cannot achieve an erection naturally, erection can be induced by injecting saline solution into the corpus cavernosum after placing a tourniquet at the base of the penis. This technique should also be used during corrective surgery to be certain that the penis will be straight after the operation.

If the penis is adequate in length, the dorsal surface can be shortened by (1) excising elliptic portions of the tunica albuginea on the dorsum of the penis on either side of the midline or (2) making transverse cuts in a similar position and then closing them longitudinally, thus shortening the dorsum. Fibrous tissue found in association with the urethra and corpus spongiosum should be totally excised.

EPISPADIAS

The incidence of complete epispadias is approximately 1 in 120,000 males and 1 in 450,000 females. The urethra is displaced dorsally, and classification is based on its position in males. In glandular epispadias, the urethra opens on the dorsal aspect of the glans, which is broad and flattened. In the penile type, the urethral meatus, which is often broad and gaping, is located between the pubic symphysis and the coronal sulcus. A distal groove usually extends from the meatus through the splayed glans. The penopubic type has the urethral opening at the penopubic junction, and the entire penis has a distal dorsal groove extending through the glans.

Patients with glandular epispadias seldom have urinary incontinence. However, with penopubic and penile epispadias, incontinence is present in 95% and 75% of cases, respectively.

Females with epispadias have a bifid clitoris and separation of the labia. Most are incontinent.

Urinary incontinence is a common problem because of maldevelopment of the urinary sphincters. Dorsal curvature of the penis (dorsal chordee) is also present (Figure 41–3). The pubic bones are separated as in exstrophy of the bladder. Epispadias is a mild form of bladder exstrophy, and in severe cases, exstrophy and epispadias coexist.

Surgery is required to correct the incontinence, remove the chordee to straighten the penis, and extend the urethra out onto the glans penis. Repair of the urinary sphincter has not been very successful. Chordee excision and urethroplasty with advancement of the meatus have been successful in achieving acceptable cosmetic and functional results. Bladder augmentation combined with the artificial sphincter may be required in patients in whom incontinence cannot be corrected.

ACQUIRED DISEASES AND DISORDERS OF THE PENIS AND MALE URETHRA

PRIAPISM

Priapism is an uncommon condition of prolonged erection. It is usually painful for the patient, and no sexual excitement or desire is present. The disorder is idiopathic in 60% of cases, while the remaining 40% of cases are associated with diseases (eg, leukemia, sickle cell disease, pelvic tumors, pelvic infections), penile trauma, spinal cord trauma, or use of medications (trazodone). Currently, intracavernous injection therapy for impotence may be the most common cause. Although the idiopathic type often is initially associated with prolonged sexual stimulation, cases of priapism due to the other causes are unrelated to psychic sexual excitement.

Priapism may be classified into high- and low-flow types. High-flow priapism (nonischemic) usually occurs secondary to perineal trauma, which injures the central penile arteries and results in loss of penile blood flow regulation. Aneurysms of one or both central arteries have been observed. Aspiration of penile blood for blood gas determination demonstrates high oxygen and normal carbon dioxide levels. Arteriography is useful to demonstrate aneurysms that will respond to embolization; erectile function is usually preserved.

The patient with low-flow priapism (ischemic) usually presents with a history of several hours of painful erection. The glans penis and corpus spongiosum are soft and uninvolved in the process. The corpora cavernosa are tense with congested blood and tender to palpation. The current theories regarding the mechanism of priapism remain in debate, but most authorities believe the major abnormality to be physiologic obstruction of the venous drainage. This obstruction causes buildup of highly viscous, poorly oxygenated blood (low O_2, high CO_2) within the corpora cavernosa. If the process continues for several days, interstitial edema and fibrosis of the corpora cavernosa will develop, causing impotence.

Ischemic priapism must be considered a urologic emergency. Epidural or spinal anesthesia can be used. The sludged blood can then be evacuated from the corpora cavernosa through a large needle placed through the glans. The addition of adrenergic agents administered via intracavernous irrigation has proved helpful. Monitoring intracavernous pressure ensures that recurrence is not imminent. Multiple wedges of tissue can be removed with a biopsy needle to create a shunting fistula between the glans penis and corpora cavernosa. This technique, which has been very successful, provides an internal fistula to keep the corpora cavernosa decompressed. To maintain continuous fistula drainage, pressure should be exerted intermittently (every 15 minutes) on the body of the penis. The patient can do this manually after he has recovered from anesthesia.

If the shunt described fails, another shunting technique may be used by anastomosing the superficial dorsal vein to the corpora cavernosa. Other effective shunting methods are corpora cavernosa to corpus spongiosum shunt by perineal anastomosis, saphenous vein → corpora cavernosa shunt, and pump decompression.

Patients with sickle cell disease have benefited from massive blood transfusions, exchange transfusions, or both. Hyperbaric oxygen also has been suggested for these patients. Patients with leukemia should receive prompt chemotherapy. Appropriate management of any underlying cause should be instituted without delay. Such treatment should not prevent aggressive management of the priapism if the erection persists for several hours.

Impotence is the worst sequel of priapism. It is more common after prolonged priapism (several days). Early recognition (within hours) and prompt treatment of priapism offer the best opportunity to avoid this major problem.

PEYRONIE'S DISEASE

Peyronie's disease (plastic induration of the penis) was first described in 1742 and is a well-recognized clinical problem affecting middle-aged and older men. Patients present with complaints of painful erection, curvature of the penis, and poor erection distal to the involved area. The penile deformity may be so severe that it prevents satisfactory vaginal penetration. The patient has no pain when the penis is in the nonerect state.

Examination of the penile shaft reveals a palpable dense, fibrous plaque of varying size involving the tunica albuginea. The plaque is usually located near the dorsal midline of the shaft. Multiple plaques are sometimes seen. In severe cases, calcification and ossification are noted and confirmed by radiography. Although the cause of Peyronie's disease remains obscure, the dense fibrous plaque is microscopically consistent with findings in severe vasculitis. The condition has been noted in association with Dupuytren's contracture of the tendons of the hand, in which the fibrosis resembles that of Peyronie's disease when examined microscopically.

Spontaneous remission occurs in about 50% of cases. Initially, observation and emotional support are advised. If remission does not occur, *p*-aminobenzoic acid powder or tablets or vitamin E tablets may be tried for several months. However, these medications have limited success. In recent years, various operative procedures have been used in refractory cases. Excision of the plaque with replacement with a dermal or vein graft has been successful, as has the use of tunica vaginalis grafts after plaque incision. Other authors have incised the plaque and inserted penile prostheses in the corpora cavernosa. Additional methods include radiation therapy and injection of steroids, dimethyl sulfoxide, or parathyroid hormone into the plaque. The success of such treatments is poorly documented.

PHIMOSIS

Phimosis is a condition in which the contracted foreskin cannot be retracted over the glans. Chronic infection from poor local hygiene is its most common cause. Most cases occur in uncircumcised males, although excessive skin left after circumcision can become stenotic and cause phimosis. Calculi and squamous cell carcinoma may develop under the foreskin. Phimosis can occur at any age. In diabetic older men, chronic balanoposthitis may lead to phimosis and may be the initial presenting complaint. Children younger than 2 years seldom have true phimosis; their relatively narrow preputial opening gradually widens and allows for normal retraction of foreskin over the glans. Circumcision for phimosis should be avoided in children requiring general anesthesia; except in cases with recurrent infections, the procedure should be postponed until the child reaches an age when local anesthesia can be used.

Edema, erythema, and tenderness of the prepuce and the presence of purulent discharge usually cause the patient to seek medical attention. Inability to retract the foreskin is a less common complaint.

The initial infection should be treated with broad-spectrum antimicrobial drugs. The dorsal foreskin can be slit if improved drainage is necessary. Circumcision, if indicated, should be done after the infection is controlled.

PARAPHIMOSIS

Paraphimosis is the condition in which the foreskin, once retracted over the glans, cannot be replaced in its normal position. This is due to chronic inflammation under the redundant foreskin, which leads to contracture of the preputial opening (phimosis) and formation of a tight ring of skin when the foreskin is retracted behind the glans. The skin ring causes venous congestion leading to edema and enlargement of the glans, which worsen the condition. As the condition progresses, arterial occlusion and necrosis of the glans may occur.

Paraphimosis usually can be treated by firmly squeezing the glans for 5 minutes to reduce the tissue edema and decrease the size of the glans. The skin can then be drawn forward over the glans. Occasionally, the constricting ring requires incision under local anesthesia. Antibiotics should be administered and circumcision should be done after inflammation has subsided.

CIRCUMCISION

Although circumcision is routinely performed in some countries and communities for religious or cultural reasons, it is seldom necessary if adequate penile cleanliness and good hygiene can be maintained. There is a higher incidence of penile carcinoma in uncircumcised males, but chronic infection and poor hygiene are usually underlying factors in such instances. Circumcision is indicated in patients with infection, phimosis, or paraphimosis (see preceding sections). Circumcision has been shown to reduce rates of HIV transmission in Sub-Saharan Africa. Widespread efforts to perform male circumcisions in sexually active adults are underway.

URETHRAL STRICTURE

Acquired urethral stricture is common in men but rare in women. (Congenital urethral stricture is discussed earlier in the chapter.) Most acquired strictures are due to infection or trauma. Although gonococcal urethritis is seldom a cause of stricture today, infection remains a major cause—particularly infection from long-term use of indwelling urethral catheters. Large catheters and instruments are more likely than small ones to cause ischemia and internal trauma. External trauma, for example, pelvic fractures (see Chapter 18), can partially or completely sever the membranous urethra and cause severe and complex strictures. Straddle injuries can produce bulbar strictures.

Urethral strictures are fibrotic narrowings composed of dense collagen and fibroblasts. Fibrosis usually extends into the surrounding corpus spongiosum, causing spongiofibrosis. These narrowings restrict urine flow and cause dilation of the proximal urethra and prostatic ducts. Prostatitis is a common complication of urethral stricture. The bladder muscle may become hypertrophic, and increased residual urine may be noted. Severe, prolonged obstruction can result in decompensation of the ureterovesical junction, reflux, hydronephrosis, and renal failure. Chronic urinary stasis renders the patient more vulnerable to infection. Urethral fistulas and periurethral abscesses commonly develop in association with chronic, severe strictures.

▶ Clinical Findings

A. Symptoms and Signs

A decrease in urinary stream is the most common complaint. Spraying or double stream is often noted, as is postvoiding dribbling. Chronic urethral discharge, occasionally a major complaint, is likely to be associated with chronic prostatitis. Acute cystitis or symptoms of infection are seen at times. Acute urinary retention seldom occurs unless infection or prostatic obstruction develops. Urinary frequency and mild dysuria may also be initial complaints.

Induration in the area of the stricture may be palpable. Tender enlarged masses along the urethra usually represent periurethral abscesses. Urethrocutaneous fistulas may be present. The bladder may be palpable if there is chronic retention of urine.

B. Laboratory Findings

If urethral stricture is suspected, urinary flow rates should be determined. The patient is instructed to accumulate urine until the bladder is full and then begin voiding; a 5-second collection of urine should be obtained during midstream maximal flow and its volume recorded. After the patient repeats this procedure 8–10 times over several days in a relaxed atmosphere, the mean peak flow can be calculated. With strictures creating significant problems, the flow rate will be <10 mL/s (normal 20 mL/s).

Urine culture may be indicated. The midstream specimen is usually bacteria-free, with some pyuria (8–10 white blood cells [leukocytes] per high-power field) in a carefully obtained first aliquot of urine. If the prostate is infected, bacteria will be present in a specimen obtained after prostatic massage. In the presence of cystitis, the urine will be grossly infected.

C. X-Ray Findings

A sequential urethrogram and voiding cystourethrogram will demonstrate the location and extent of the stricture. Sonography has also been a useful method of evaluating the urethral stricture. Urethral fistulas and diverticula are sometimes noted. Vesical stones, trabeculations, or diverticula may also be seen.

D. Instrumental Examination

Urethroscopy allows visualization of the stricture. Small-caliber strictures prevent passage of the instrument through the area. Direct visualization and sonourethrography aid in determining the extent, location, and degree of scarring. Additional areas of scar formation adjacent to the stricture may be detected by urethroscopy.

The stricture can be calibrated by passage of bougies à boule.

Differential Diagnosis

Benign or malignant prostatic obstruction can cause symptoms similar to those of stricture. After prostatic surgery, bladder neck contracture can develop and induce stricture-like symptoms. Rectal examination and panendoscopy adequately define such abnormalities of the prostate. Urethral carcinoma is often associated with stricture; urethroscopy demonstrates a definite irregular lesion, and biopsy establishes the diagnosis of carcinoma.

Complications

Complications include urinary retention, urinary reflux, chronic prostatitis, cystitis, chronic urinary infection, diverticula, urethrocutaneous fistulas, periurethral abscesses, urethral carcinoma, and renal failure. Vesical calculi may develop from chronic urinary stasis and infection.

Treatment

A. Specific Measures

1. Dilation—Dilation of urethral strictures is seldom curative, but it fractures the scar tissue of the stricture and temporarily enlarges the lumen. As healing occurs, the scar tissue re-forms.

Dilation may initially be required because of severe symptoms of acute or chronic retention of urine. The urethra should be liberally lubricated with a water-soluble medium before instrumentation. Various methods of dilating a urethral stricture are available, including filiform and followers, sounds, and balloon dilation.

An alternative method of urethral dilation employs Van Buren urethral sounds. These instruments are best used by an experienced urologist familiar with the size and extent of the stricture involved. First, a 22Fr sound should be passed down to the stricture site and gentle pressure applied. If this fails, a 20Fr sound should be used. Smaller sounds should be used with care, because they can easily perforate the urethral wall and produce false passages. Bleeding and pain are major problems caused by dilation.

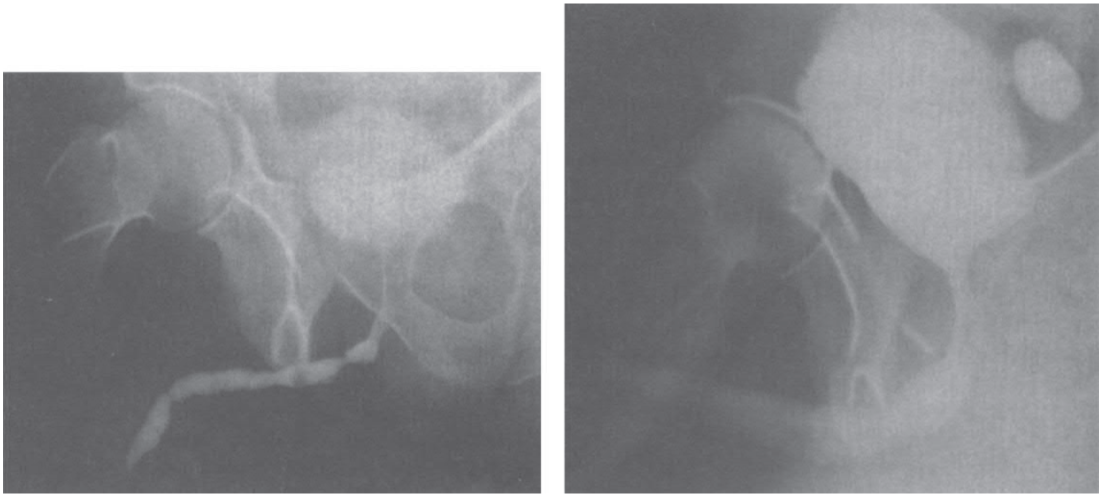
2. Urethrotomy under endoscopic direct vision—Lysis of urethral strictures can be accomplished using a sharp knife attached to an endoscope. The endoscope provides direct vision of the stricture during cutting. A wire can be passed through the stricture and used as a guide during lysis. The stricture is usually incised circumferentially with multiple incisions. A 22Fr instrument should pass with ease. A catheter is left in place for a short time to prevent bleeding and pain. Results of this procedure have been satisfactory in short-term follow-up in 70–80% of patients, but long-term success rates are much lower. The procedure has several advantages: (a) minimal anesthesia is required—in some cases, only topical anesthesia combined with sedation; (b) it is easily repeated if the stricture recurs; and (c) it is very safe, with few complications. Direct-vision urethrotomy is often preferential to dilation because the area of stenosis can be precisely instrumented with less injury to surrounding healthy urethra.

3. Surgical reconstruction—If urethrotomy under direct vision fails, open surgical repair should be performed. Short strictures (≤2 cm) of the bulbar urethra should be completely excised and primary anastomosis done. If possible, the segment to be excised should extend 1 cm beyond each end of the stricture to allow for removal of any existing spongiofibrosis and improve postoperative healing.

Strictures >2 cm in length can be managed by patch graft urethroplasty. The urethra is incised in the midline for the full length of the stricture plus an additional 0.5 cm proximal and distal to its ends. A full-thickness skin graft is obtained—preferably from buccal mucosa—and all subcutaneous tissues are carefully removed. The graft is then tailored to cover the defect and meticulously sutured into place (Figure 41–4).

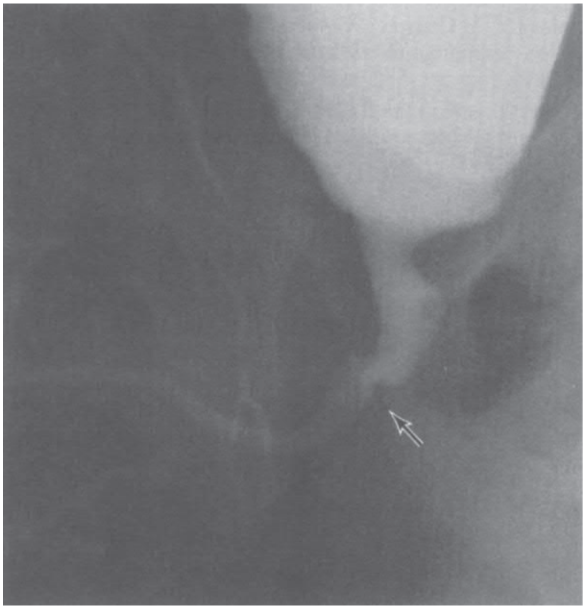
In very long, densely fibrotic strictures, the distal penile fasciocutaneous flap technique has been successful in >80% of cases. This single-stage procedure can be combined with buccal mucosa grafting in panurethral strictures. In adults, grafts from buccal mucosa should be applied with an onlay technique in the bulbar region of the urethra to maximize graft vascularization from the corpus spongiosum. Either a dorsal or ventral approach for graft placement can used.

Strictures involving the membranous urethra ordinarily result from external trauma (see Chapter 17) and present problems in reconstruction. Most can be corrected by a perineal approach with excision of the urethral rupture defect and direct anastomosis of the bulbar urethra to the prostatic urethra (Figure 41–5). At times, partial pubectomy from the perineal approach can be done to improve urethral approximation without tension on the anastomosis. Rarely, total pubectomy combined with the perineal approach is required to accomplish the direct end-to-end anastomosis.



▲ **Figure 41–4.** ***Left:*** Urethrogram demonstrating multiple anterior urethral strictures. ***Right:*** Voiding cystourethrogram following a patch skin graft of 14 cm in the same patient. There are no residual strictures.

These single-stage procedures have a high success rate and create a urethra free of hair—a major problem seen with two-stage procedures. Although seldom required, two-stage procedures are important reconstructive techniques to be considered in complex urethral strictures.



▲ **Figure 41–5.** Voiding urethrogram following repair of traumatic posterior urethral stricture. *Arrow* indicates that area of repair is stricture-free.

B. Treatment of Complications

Urinary tract infection in patients with strictures requires specific antimicrobial therapy, followed by long-term prophylactic therapy until the stricture has been corrected. Periurethral abscesses require drainage and use of antimicrobial drugs. Urethral fistulas usually require surgical repair.

▶ Prognosis

A stricture should not be considered “cured” until it has been observed for at least 1 year after therapy, since it may recur at any time during that period. Strictures have been observed to recur decades after urethroplasty and patients should be made aware of this. Urinary flow rate measurements and urethrograms are helpful to determine the extent of residual obstruction.

URETHRAL CONDYLOMATA ACUMINATA (URETHRAL WARTS)

Condylomata acuminata are uncommon in the urethra and are almost always preceded by lesions on the skin. They are wartlike papillomas caused by a human papilloma virus (HPV) and are usually transmitted by direct sexual contact but may be transmitted nonsexually.

Patients commonly complain of bloody spotting from the urethra and occasionally have dysuria and urethral discharge. Examination of the urethral meatus often reveals a small, protruding papilloma. If a lesion is not found in this location, the meatus should be separated with the examining fingers so that the distal urethra can be inspected. About 90% of such lesions are situated in the distal urethra. Complete urethroscopy must be done to confirm that certain other lesions do not exist.

Lesions of the meatus can be treated by local excision. A local anesthetic is applied to the area at the base of the lesions, and the pedunculated lesions are sharply incised with small scissors. The area is then fulgurated by electrocautery. Meatotomy may be indicated for excision of lesions in the fossa navicularis and glandular urethra.

Deeper lesions may be fulgurated transurethrally with a resectoscope or Bugby electrode. Recently, lesions have been successfully destroyed using a carbon dioxide or holmium laser. Laser therapy does minimal damage to the urethral mucosa, and stricture formation seems less likely with its use.

Multiple lesions have also been treated with fluorouracil, in a 5% solution or cream. The drug is instilled in the urethra for 20 minutes twice a week for 5 weeks. Care must be taken to protect the penile skin and scrotum from direct contact with the medication, since it may produce severe irritation.

Lesions may become infected and ulcerated. This suggests carcinoma, and histopathologic confirmation of the diagnosis should be obtained. Rarely, giant condylomata (Buschke–Löwenstein tumors) involving the glans penis and often the urethra may be seen. Such lesions suggest carcinoma, and a biopsy must be performed. Surgical excision is the treatment of choice.

The sexual partner must also be examined and treated if necessary. Patients without condyloma should be encouraged to be vaccinated against HPV.

STENOSIS OF THE URETHRAL MEATUS

Newborns are often suspected of having meatal stenosis of some degree. This condition is believed to be secondary to ammonia dermatitis following circumcision and resulting in prolonged irritative meatitis.

Calibration is important, since the visual appearance of the meatus does not correlate well with its actual size. The urethra should easily accept the tip of an 8Fr pediatric feeding tube. The significance of metal stenosis is debated, but a meatal caliber <5Fr in children <10 years of age is an indication for meatotomy.

PENILE PHLEBOTHROMBOSIS AND LYMPHATIC OCCLUSION

Superficial veins and lymphatic vessels of the dorsal penile shaft just proximal to the corona may become irritated and inflamed. A careful history usually indicates that minor trauma to the area (eg, from prolonged sexual intercourse) has occurred. Examination reveals a tender, indurated, cordlike structure on the distal penile shaft. Slight erythema may be present.

For clinical purposes, there is no need to distinguish lymphatic and venous causes, since both penile phlebothrombosis and lymphatic occlusion will resolve spontaneously. The patient must be reassured.

BIBLIOGRAPHY

Congenital Anomalies

Penis and Urethra

Akman Y et al: Penile anatomy under the pubic arch: Reconstructive implications. J Urol 2001;166:225.

Barbagli G: Editorial comment on: Surgical treatment of 31 complex traumatic posterior urethral strictures associated with urethrorectal fistulas. Eur Urol 2010;57(3):520–521.

Confer SD et al: Megacystis with an anterior urethral valve: Case report and review of literature. J Pediatr Urol 2010;6(5):459–462.

de Oliveira MC et al: Surgical treatment of penile duplication. J Pediatr Urol 2010;6(3):257.e1–257.e3.

Fine MS et al: Posterior urethral valve treatments and outcomes in children receiving kidney transplants. J Urol 2011;185 (6 Suppl):2507–2511.

Gad YZ et al: 5 alpha-reductase deficiency in patients with micropenis. J Inherit Metab Dis 1997;20:95.

Ishii T et al: The effect of intramuscular testosterone enanthate treatment on stretched penile length in prepubertal boys with hypospadias. Urology 2010;76(1):97–100.

Sarhan OM et al: Posterior urethral valves: Multivariate analysis of factors affecting the final renal outcome. J Urol 2011;185(6 Suppl): 2491–2495.

Tsang S: When size matters: A clinical review of pathological micropenis. J Pediatr Health Care 2010;24(4):231–240 (review).

Wan J, Rew KT: Common penile problems. Prim Care 2010; 37(3):627–642, x (review).

Wessells H et al: Penile length in the flaccid and erect states: Guidelines for penile augmentation. J Urol 1996;156:995.

Yanai T et al: Minimally invasive repair of hypospadiac urethral duplication. Pediatr Surg Int 2011;27(1):115–118.

Hypospadias

Acimi S: Comparative study of two techniques used in distal hypospadias repair: Tubularized incised plate (Snodgrass) and tubularized urethral plate (Duplay). Scand J Urol Nephrol 2011;45(1):68–71.

Barbagli G et al: Retrospective descriptive analysis of 1,176 patients with failed hypospadias repair. J Urol 2010;183(1):207–211.

Baskin LS: Hypospadias and urethral development. J Urol 2000; 163:951.

Bhangoo A et al: Isolated micropenis reveals partial androgen insensitivity syndrome confirmed by molecular analysis. Asian J Androl 2010;12(4):561–566.

Castagnetti M, El-Ghoneimi A: Surgical management of primary severe hypospadias in children: Systematic 20-year review. J Urol 2010;184(4):1469–1474.

Hensle TW et al: Hypospadias repair in adults: Adventures and misadventures. J Urol 2001;165:77.

Powell CR et al: Comparison of flaps versus grafts in proximal hypospadias surgery. J Urol 2000;163:1286.

Roberts J: Hypospadias surgery past, present and future. Curr Opin Urol 2010;20(6):483–489.

Snodgrass W: Hypospadias reporting—How good is the literature? J Urol 2010;184(4):1255–1256.

Thorup J et al: What is new in cryptorchidism and hypospadias—A critical review on the testicular dysgenesis hypothesis. J Pediatr Surg 2010;45(10):2074–2086.

Wan J, Rew KT: Common penile problems. Prim Care 2010;37(3): 627–642.

Ziada A et al: Outcomes of hypospadias repair in older children: A prospective study. J Urol 2011;185(6 Suppl):2483–2485.

Epispadias

Baird AD et al: Reconstructive lower urinary tract surgery in incontinent adolescents with exstrophy/epispadias complex. Urology 2005;66:636.

Ben-Chaim J, Gearhart JP: Current management of bladder exstrophy. Scand J Urol Nephrol 1997;31:103.

Gearhart JP: Re: Results of complete penile disassembly for epispadias repair in 42 patients. J Urol 2004;171:2386.

Grady RW, Mitchell ME: Management of epispadias. Urol Clin North Am 2002;29:349.

Hammouda HM: Results of complete penile disassembly for epispadias repair in 42 patients. J Urol 2003;170:1963.

Acquired Diseases and Disorders of the Penis and Male Urethra

Park S et al: Extramammary Paget's disease of the penis and scrotum: Excision, reconstruction and evaluation of occult malignancy. J Urol 2001;166:2112.

Rosenstein D, McAninch JW: Urologic emergencies. Med Clin North Am 2004;88:495.

Priapism

Chinegwundoh F, Anie KA: Treatments for priapism in boys and men with sickle cell disease. Cochrane Database Syst Rev 2004;18(4):CD004098.

Costa WS et al: Structural analysis of the corpora cavernosa in patients with ischaemic priapism. BJU Int 2010;105(6):838–840; discussion 840.

Montague DK et al: American Urological Association guideline on the management of priapism. J Urol 2003;170:1318.

Montague DK: Sexual dysfunction: Immediate penile prosthesis for acute ischemic priapism. Nat Rev Urol 2010;7(4):187–188.

Shrewsberry A et al: Recent advances in the medical and surgical treatment of priapism. Curr Urol Rep 2010;11(6):405–403 (review).

Stember DS, Mulhall JP: Ischemic priapism and implant surgery with sharp corporal fibrosis excision. J Sex Med 2010;7(6):1987–1990; quiz 1991.

Tabibi A et al: Erectile function and dysfunction following low flow priapism: A comparison of distal and proximal shunts. Urol J 2010;7(3):174–177.

Volkmer BG et al: Prepubertal high flow priapism: Incidence, diagnosis and treatment. J Urol 2001;166:1018.

Peyronie's Disease

Breyer BN et al: Are sonographic characteristics associated with progression to surgery in men with Peyronie's disease? J Urol 2010;183(4):1484–1488.

Chung E et al: Five-year follow-up of Peyronie's graft surgery: Outcomes and patient satisfaction. J Sex Med 2011;8(2):594–600.

Eisenberg ML et al: Tunica-sparing ossified Peyronie's plaque excision. BJU Int 2011;107(4):622–625.

Heidari M et al: Evaluation of intralesional injection of verapamil in treatment of Peyronie's disease. J Pak Med Assoc 2010;60(4): 291–293.

Hellstrom WJ: Medical management of Peyronie's disease. J Androl 2009;30(4):397–405.

Mulhall JP et al: Basic fibroblast growth factor expression in Peyronie's disease. J Urol 2001;165:409.

Seftel AD: Incidentally diagnosed Peyronie's disease in men presenting with erectile dysfunction. J Urol 2005;173:2076.

Simonato A et al: Penile dermal flap in patients with Peyronie's disease: Long-term results. J Urol 2010;183(3):1065–1068.

Tal R et al: Peyronie's disease following radical prostatectomy: Incidence and predictors. J Sex Med 2010;7(3):1254–1261.

Wilson SK et al: Long-term followup of treatment for Peyronie's disease: Modeling the penis over an inflatable penile prosthesis. J Urol 2001;165:825.

Phimosis

Hayashi Y et al: Prepuce: Phimosis, paraphimosis, and circumcision. ScientificWorldJournal 2011;11:289–301.

Minhas S et al: Penile cancer—prevention and premalignant conditions. Urology 2010;76(2 Suppl 1):S24–S35.

Nobre YD et al: To circ or not to circ: Clinical and pharmacoeconomic outcomes of a prospective trial of topical steroid versus primary circumcision. Int Braz J Urol 2010;36(1):75–85.

Pieretti RV et al: Late complications of newborn circumcision: A common and avoidable problem. Pediatr Surg Int 2010; 26(5):515–518.

Paraphimosis

Olson C: Emergency treatment of paraphimosis. Can Fam Physician 1998;44:1253.

Circumcision

Fitzgerald DW et al: An Ad5-vectored HIV-1 vaccine elicits cell-mediated immunity but does not affect disease progression in HIV-1-infected male subjects: Results from a randomized placebo-controlled trial (the Step study). J Infect Dis 2011;203(6):765–772.

Mahanta J et al: Circumcision and herpes simplex virus-2 infection among spouses. Sex Transm Infect 2010;86(7):487.

Mokhless IA et al: Penile advancement and lengthening for the management of post-circumcision traumatic short penis in adolescents. Urology 2010;76(6):1483–1487.

Wawer MJ et al: Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: A randomised trial in Rakai, Uganda. Lancet 2011;377(9761):209–218.

Urethral Stricture

Anger JT et al: Trends in stricture management among male Medicare beneficiaries: Underuse of urethroplasty? Urology 2011;77(2):481–485.

Breyer BN et al: Multivariate analysis of risk factors for long-term urethroplasty outcome. J Urol 2010;183(2):613–617.

Burks FN, Santucci RA: Complicated urethroplasty: A guide for surgeons. Nat Rev Urol 2010;7(9):521–528.

Chapple C: Anterior urethral surgery: Current concepts and future directions. Eur Urol 2010;58(1):42–45.

Ching CB et al: The Cleveland Clinic experience with adult hypospadias patients undergoing repair: Their presentation and a new classification system. BJU Int 2011;107(7):1142–1146.

Erickson BA et al: The use of uroflowmetry to diagnose recurrent stricture after urethral reconstructive surgery. J Urol 2010; 184(4): 1386–1390.

Lumen N et al: Ventral longitudinal stricturotomy and transversal closure: The Heineke-Mikulicz principle in urethroplasty. Urology 2010;76(6):1478–1482.

Mundy AR, Andrich DE: Urethral strictures. BJU Int 2011;107(1): 6–26.

Myers JB, McAninch JW: Perineal urethrostomy. BJU Int 2011;107(5): 856–865.

Myers JB, McAninch JW: Surgery illustrated—surgical atlas perineal urethrostomy. BJU Int 2011;107(5):856–857.

Santucci R, Eisenberg L: Urethrotomy has a much lower success rate than previously reported. J Urol 2010;183(5):1859–1862.

Schwentner C et al: Anterior urethral reconstruction using the circular fasciocutaneous flap technique: Long-term follow-up. World J Urol 2011;29(1):115–120.

Whitson JM et al: Long-term efficacy of distal penile circular fasciocutaneous flaps for single stage reconstruction of complex anterior urethral stricture disease. J Urol 2008;179(6):2259–2264.

Urethral Condylomata Acuminata (Urethral Warts)

Stefanaki C et al: Prognostic factors for the response to treatment in males with genital warts. J Eur Acad Dermatol Venereol 2009;23(10):1156–1160.

Penile Phlebothrombosis and Lymphatic Occlusion

Conkbayir I et al: Superficial dorsal penile vein thrombosis (Mondor disease of the penis) involving the superficial external pudendal vein: Color Doppler sonographic findings. J Ultrasound Med 2010;29(8):1243–1245.

Disorders of the Female Urethra

42

Donna Y. Deng, MD, MS

CONGENITAL ANOMALIES OF THE FEMALE URETHRA

DISTAL URETHRAL STENOSIS IN INFANCY AND CHILDHOOD (SPASM OF THE EXTERNAL URINARY SPHINCTER) AND DYSFUNCTIONAL VOIDING

Congenital anomalies of the urethra are rare. These include urethral valves (posterior and anterior), urethral atresia, congenital urethral stenosis, cloacal malformations, female epispadias, bladder–sphincter dysfunction without neurologic abnormality, and congenital urethrovaginal fistula. The purely anatomically based obstructive urethral abnormalities are found chiefly in males (posterior urethral valves). The largest population-based prevalence study of lower urinary tract obstruction showed 3.3 urethral abnormalities in 10,000 births. Most of these were due to posterior urethral valves, with 1.9 in 10,000 births (Malin et al, 2012). There are only six reported cases of congenital urethrovaginal fistulas; the most recently reported ones are due to a low transverse vaginal septum (Amer et al, 2016).

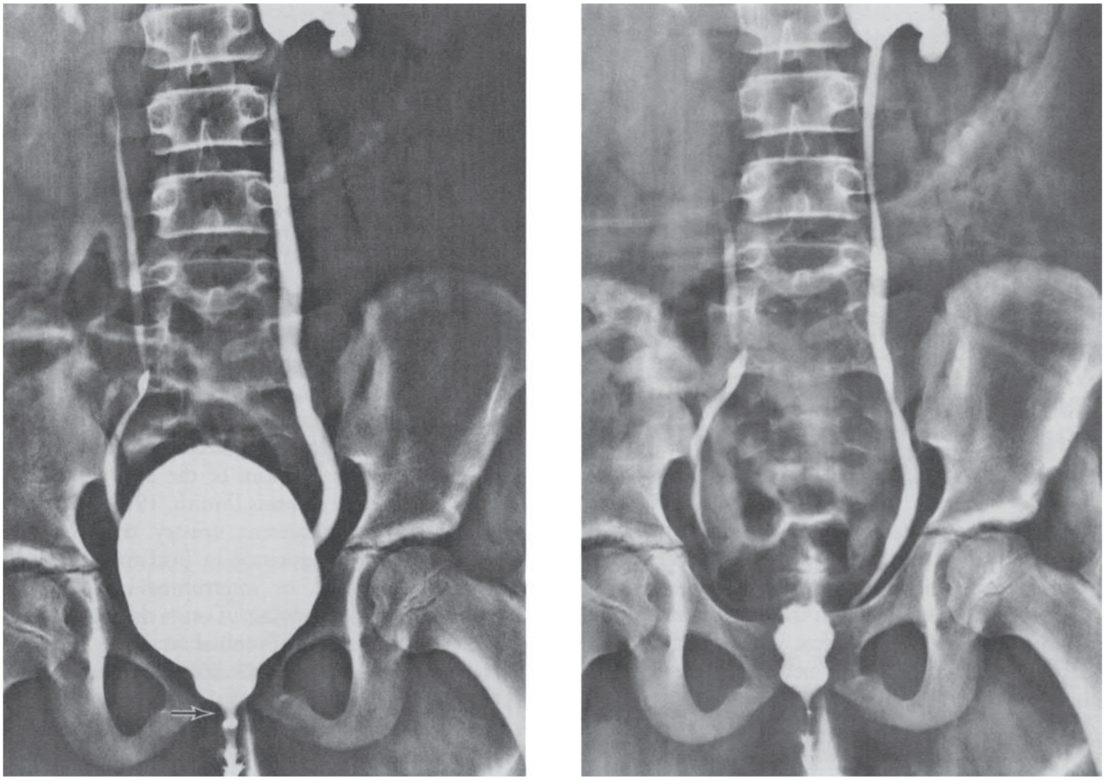
Congenital urethral stenosis is rare. The more common lower urinary tract obstruction in girls is dysfunctional voiding. Clinical presentation is similar in both. This includes hesitancy in initiating micturition, a slow and interrupted urinary stream, recurrent cystitis, and pyelonephritis. On further evaluation, the patient may exhibit vesicoureteral reflux. Enuresis and involuntary loss of urine during the day are common complaints. Abdominal straining may be required in order to void. Small amounts of residual urine are found, which impair the vesical defense mechanism. A voiding cystourethrogram may reveal an open bladder neck and ballooning of the proximal urethra (Figure 42–1).

In girls with congenital distal urethral stenosis, the obstruction is due to secondary spasm of the striated external sphincter rather than bladder neck obstruction. Lyon and Tanagho (1965) found that the distal urethral ring calibrates at 14Fr at age 2 years and at 16Fr between the ages of 4 and 10 years. From the hydrodynamic perspective, even though such a stenotic area should not be obstructive, almost all observers agree that dilatation of the ring does relieve symptoms in these children and that it results in cure or amelioration of persistent infection or vesical dysfunction in 80% of cases (Kondo et al, 1994). Tanagho et al (1971) measured pressures in the bladder and in the proximal and midurethra simultaneously in symptomatic girls and found high resting pressures, some as high as 200 cm of water (normal, 100 cm of water) in the midurethral segment. Attempts at voiding caused intravesical pressures as high as 225 cm of water (normal, 30–40 cm of water) to develop. Under the drug curare, the urethral closing pressures dropped to normal (40–50 cm of water), proving that these obstructing pressures were caused by spasm of the striated sphincter muscle. When the distal urethral ring was treated and symptoms abated, repeat pressure studies showed normal midurethral and intravesical voiding pressures. It seems clear, therefore, that the likely cause of urinary problems in young girls is spasm of the external sphincter and not vesical neck stenosis (Smith, 1969).

The voiding cystourethrogram may reveal evidence of the distal ring, but typical findings are not always seen, particularly if the flow rate is slow. Definitive diagnosis is made by bougienage.

Historically, the simplest and least harmful treatment is dilatation with sounds up to 32–36Fr. The ring “cracks” anteriorly, with some bleeding. Recurrence of the ring is rare. The results of internal urethrotomy were poor, since incising the urethra along its entire length does not cut the external sphincter (Kaplan et al, 1973).

In the past two decades, it has been recognized that most urinary obstruction in children is due to functional, rather than neurologic or anatomic, causes of obstruction. Children must achieve adult patterns of urinary control, and disturbances can occur, especially around the time of toilet training. This



▲ **Figure 42–1.** Distal urethral stenosis with reflux spasm of voluntary urethral sphincter. ***Left:*** Voiding cystourethrogram showing bilateral vesicoureteral reflux, a wide-open vesical neck, and severe spasm of the striated urethral sphincter in the middle portion of the urethra (*arrow*) secondary to distal urethral stenosis. ***Right:*** Postvoiding film. The bladder is empty and the vesical neck open, but the dilated urethra contains radiopaque fluid proximal to the stenotic zone. Bacteria in the urethra thus can flow back into the bladder. (Used with permission from AD Amar.)

may cause a variety of symptoms that result from voiding against a voluntarily closed urethral sphincter (dysfunctional voiding). These range from severe functional obstruction with urinary retention, altered bladder anatomy, and vesicoureteral reflux (known as **Hinman's syndrome**) to less severe incomplete control of urination. They are often accompanied by bowel symptoms, such as constipation or encopresis. Treatment requires bladder retraining, including psychologic help and biofeedback, as well as restoration of normal bowel habits, including dietary changes and treatments for improved stooling.

We have come to understand and realize the importance of specialized pelvic physical therapy involving myofascial release, internal and external massage, assessment of hip or spine abnormalities that can impact the pelvic floor, neuromuscular remodulation, and most importantly, appropriate and consistent home exercise program tailored for the patient. The key point is that Kegel exercise to tighten the pelvic floor muscle is generally inappropriate and can worsen the condition. The difficulty is in the paucity of experienced pelvic physical therapists. It is nearly impossible to find one who can work with the pediatric population.

LABIAL FUSION (SYNECHIA VULVAE)

Some children with recurring urinary infection are found to have fused labia minora, which are apt to obstruct the flow of urine, causing it to pool in the vagina. Local application of estrogen cream twice daily for 2–4 weeks usually causes spontaneous separation, with minimal side effects (Aribarg, 1975; Leung et al, 2005). Forceful separation or dissection has its advocates (Christensen and Oster, 1971).

Labial fusion can be regarded as an acquired disease after puberty, caused by genital trauma (sexual abuse, vaginal delivery, surgery, etc) (Kumar et al, 2006). In cultures where "female circumcision" (female genital mutilation) is performed, this may be a relatively common complication (Adekunle et al, 1999).

ACQUIRED DISEASES OF THE FEMALE URETHRA

ACUTE URETHRITIS

Acute urethritis frequently occurs with gonorrheal (*Neisseria gonorrhoeae*) or trichomoniasis (*Trichomonas vaginalis*) infection in women, and it may occur less commonly with infection by *Chlamydia trachomatis* (approximately 25% of cases are symptomatic). Urinary symptoms are often present at the onset of the disease. Cultures and smears establish the diagnosis. Prompt cure can be achieved with antimicrobial drugs, usually to cover both gonorrhea and chlamydia, such as a combination of intramuscular ceftriaxone and oral azithromycin or doxycycline. Treatment is important, as 40% of women with untreated chlamydia infections will have pelvic inflammatory disease, which may lead to ectopic pregnancy, pelvic pain, and infertility (Simms and Stephenson, 2000).

The detergents in bubble bath and some spermicidal jellies may cause vaginitis and urethritis. Symptoms of vesical irritability may occur (Bass, 1968; Marshall, 1965).

CHRONIC URETHRITIS

Chronic urethritis is one of the most common urologic problems of females. The distal urethra normally harbors pathogens, and the risk of infection may be increased by wearing contaminated diapers, by insertion of an indwelling catheter, by spread from cervical or vaginal infections, or by intercourse with an infected partner. Urethral inflammation may also occur from the trauma of intercourse or childbirth.

▶ Clinical Findings

The urethral mucosa is reddened, quite sensitive, and often stenotic. Granular areas are often seen, and polypoid masses may be noted just distal to the bladder neck.

A. Symptoms

The symptoms resemble those of cystitis, although the urine may be clear. Complaints include burning on urination, frequency, and nocturia. Discomfort in the urethra may be felt, particularly when walking.

B. Signs

Examination may disclose redness of the meatus, hypersensitivity of the meatus and of the urethra on vaginal palpation, and evidence of cervicitis or vaginitis.

C. Laboratory Findings

When the initial and midstream urine samples are collected in separate containers, the first glass contains pus and the second does not (Marshall et al, 1970). *Ureaplasma urealyticum* (formerly called "T strains of mycoplasmas") is often identifiable in the first glass. These findings are similar to those of nongonococcal (chlamydial) urethritis in males. Clinically, the presence of white blood cells (leukocytes) in the absence of bacteria on a routine stain or culture suggests nongonococcal urethritis. In other cases, various bacteria (eg, *Streptococcus faecalis*, *Escherichia coli*) may be cultured from both the urethral washings and a specimen taken from the introitus.

D. Instrumental Examination

A catheter, bougie à boule, or sound may meet resistance because of urethral stenosis. Panendoscopy reveals redness and a granular appearance of the mucosa (Krieger, 1988). Inflammatory polyps may be seen in the proximal portion of the urethra. Cystoscopy may show increased injection of the trigone (trigonitis), which often accompanies urethritis.

▶ Differential Diagnosis

Differentiation of urethritis from cystitis depends on bacteriologic study of the urine; panendoscopy demonstrates the urethral lesion. Both urethritis and cystitis may be present. Chronic noninflammatory urethritis may be a manifestation of psychic stressors. Patients with anxiety or pain disorders may present with symptoms that are very suggestive of urethritis. Alternatively, women with longstanding symptoms may have these symptoms as an adult version of childhood voiding dysfunction (see earlier discussion). It is important to understand that chronic dysuria in the absence of a real bacteriologic source is often a manifestation of chronic pelvic pain syndrome (ie, interstitial cystitis, painful bladder syndrome).

▶ Treatment and Prognosis

Gradual urethral dilatations (up to 36Fr in adults) are indicated for true urethral stenosis; this allows for some inevitable contracture. Immergut and Gilbert (1973) prefer internal urethrotomy (Farrar et al, 1980). However, true urethral stenosis is not common in women, and diagnosis should be confirmed by cystoscopy and urethral calibration. If pelvic floor dysfunction is the underlying issue, calibration under anesthesia will show normal caliber urethra. *U. urealyticum* and chlamydial urethritis usually respond to doxycycline or azithromycin.

To emphasize, true female urethral strictures are rare. Most obstructive voiding symptoms in a woman are due to pelvic floor hypertonicity or dysfunction, and pelvic physical therapy is the key. The difficulty is in the paucity of experienced pelvic physical therapists.

ATROPHIC URETHRITIS

After physiologic (or surgical) menopause, hypoestrogenism occurs and atrophic changes take place in the vaginal mucosa, so it becomes dry and pale (Smith, 1972). Atrophic vaginitis affects 20–30% of postmenopausal women. This is likely a significant underestimation because women are unwilling to report symptoms either because of embarrassment or because they do not know that there are treatments available (Johnston et al, 2004). Similar changes develop in the lower urinary tract; these arise from the same embryologic tissues as the female reproductive organs. Some eversion of the mucosa about the urethral orifice, from atrophy of the vaginal wall, is usually seen. This is commonly misdiagnosed as caruncle.

Clinical Findings

A. Symptoms

Many postmenopausal women have symptoms of vesical irritability (burning, frequency, urgency) and stress incontinence. Dysuria may occur following contact with urine of the inflamed atrophic tissues themselves or because of the increased incidence of urinary tract infections in these women. These women may complain of vaginal and vulvar itching or tightness, discharge, or dyspareunia, and they may have bloody vaginal spotting, especially after intercourse.

B. Signs

The vaginal epithelium is dry and pale, with a decrease in the rugae. The mucosa at the urethral orifice is often reddened and hypersensitive; eversion of its posterior lip from atrophy of the urethrovaginal wall is common. Atrophic vaginitis also increases the risk for urinary tract infections, and approximately 10–15% of women older than 60 years have frequent urinary tract infections. In mice that were ovariectomized to create a postmenopausal state, there was a higher bacteriuria count, more robust inflammatory response, increased production of IL6 (pro-inflammatory cytokine), and more intracellular bacterial reservoirs.

C. Laboratory Findings

The urine is usually free of microorganisms. The diagnosis can be made by the following procedure. A dry smear of vaginal epithelial cells is stained with Lugol's solution. The slide is then washed with water and immediately examined microscopically while wet. In hypoestrogenism, the cells take up the iodine poorly and therefore acquire a yellow color. When the mucosa is normal, these cells stain a deep brown because of their glycogen content. The diagnosis may also be confirmed by a Papanicolaou smear. Postmenopausal status is associated with a higher vaginal pH, a decrease in vaginal lactobacillus colonization, and increased colonization with *E. coli*.

D. Instrumental Examination

Cystourethroscopy may demonstrate a reddened and granular urethral mucosa. Some urethral stenosis may be noted. More commonly, the mucosa at the meatus is reddened, but the remainder of the urethra is quite normal.

Differential Diagnosis

Atrophic urethritis is often mistaken for urethral caruncle. Eversion of the posterior lip of the urinary meatus is evident in both conditions; however, a hypersensitive vascular mass is not present in atrophic urethritis.

Treatment

Atrophic urethritis responds well to local estrogen treatment to the vagina (Sturdee and Panay, 2010). There are several formulations available: conjugated equine estrogen cream, a sustained-release intravaginal estradiol ring that delivers a low level of estradiol over a 3-month period, or a low-dose vaginal estradiol tablet. Vaginal estrogen replacement is associated with increased vaginal colonization with lactobacilli and lowers vaginal pH. Vaginal lactobacilli may protect against colonization with uropathogens. Local application has the advantage of minimal change of systemic blood level and thus avoids the side effects associated with systemic hormone therapy. There are insufficient data to recommend annual endometrial surveillance in asymptomatic women using local estrogens. However, for those who have had breast or gynecologic cancer, consultation with their oncologist is important.

Prognosis

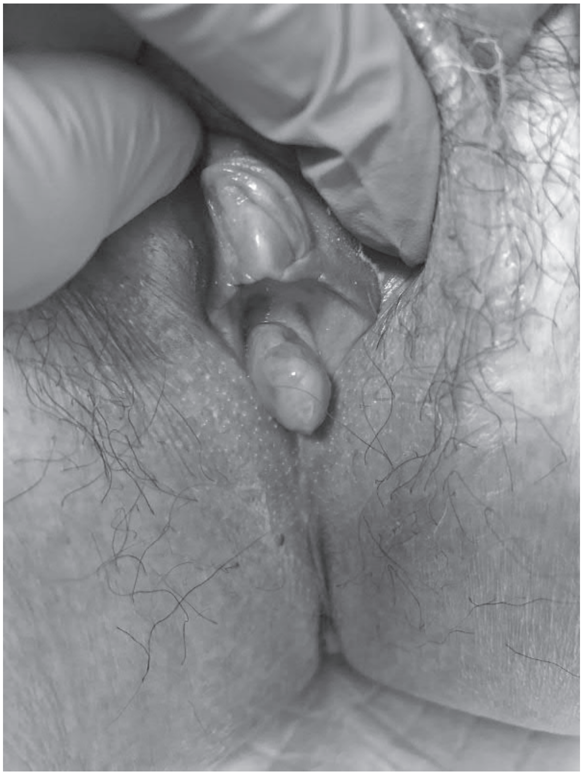
Topical vaginal estrogen is an effective treatment in postmenopausal women with recurrent infections (Quinlivan, 1965). In a controlled trial, patients treated with the estrogen cream averaged 0.5 infections per year, compared with about 6.0 infections per year in women who were not treated (Raz and Stamm, 1993). Another randomized, open-label, parallel-group study showed the estradiol vaginal ring to decrease recurrent UTI in postmenopausal women (Eriksen, 1999).

URETHRAL CARUNCLE

Urethral caruncle is an inflammatory lesion of the distal urethra. It is most commonly diagnosed in postmenopausal women. The appearance is a reddish, raspberry-like, friable exophytic mass involving the posterior lip of the external urinary meatus. Microscopically, it consists of connective tissue containing many inflammatory cells and blood vessels and is covered by an epithelial layer (Lee et al, 1995).

Clinical Findings

Symptoms include pain on urination, pain with intercourse, and bloody spotting from even mild trauma. A sessile or pedunculated red, friable, tender mass is seen at the posterior lip of the meatus (Figure 42–2). Less commonly they may cause voiding symptoms. Rarely, the lesions may thrombose, resulting in a discolored periurethral mass. Chronic irritation contributes to hemorrhage, necrosis, and inflammatory growth of the tissue. It should *not* be circumferential.



▲ **Figure 42–2.** Urethral caruncle. The fleshy lobulated mass is emanating from the urethral meatus posteriorly. The meatal lumen is the sliver above the mass.

Differential Diagnosis

If the lesion is atypical in appearance or behavior, excision or biopsy is warranted. Carcinoma of the urethra may involve the urethral meatus. Palpation reveals definite induration. Atrophic urethritis is often associated with a polypoid reaction of the urinary meatus and in fact is the most common cause of masses in this region. The diagnosis can be made by verifying the patient's hypoestrogenic status and by demonstrating a favorable response to estrogen replacement therapy. Biopsy should be done if doubt exists (Neilson et al, 1989; Young et al, 1996). Other conditions that have been reported to coexist with or mimic urethral caruncles include intestinal metaplasia, tuberculosis, melanoma, and lymphoma (Willett and Lack, 1990; Indudhara et al, 1992; Lopez et al, 1993; Atalay et al, 1998).

Treatment

There is a lack of literature supporting the optimal treatment of urethral caruncles. Initial conservative management includes topical estrogen cream and/or anti-inflammatory creams, and sitz baths. If the lesion is large or symptomatic and refractory to conservative treatment, simple excision can be performed. The mucosa can be reapproximated with absorbable suture if a large defect remains. In most cases, the urethral mucosa will heal around a urethral catheter.

Prognosis

True caruncle is usually cured by excision, but in a few instances, it does recur.

URETHRAL PROLAPSE

Prolapse of the female urethra is a circumferential eversion of the urethral mucosa at the level of the urethral meatus. It occurs most often in prepubertal girls and in postmenopausal women (Rudin et al, 1997). In children, it is often a result of Valsalva voiding or constipation. Eversion of the mucosa can then occur as a result of loose connections between the inner longitudinal and outer circular muscle layers of the distal urethra (Lowe et al, 1986; Valerie et al, 1999). Etiology is less clear for postmenopausal women. It has been epidemiologically linked to estrogen deficiency (Desai and Cohen, 1997). The most common initial complaint is bleeding or spotting. Some can become painful or cause urinary symptoms. The appearance is a beefy red doughnut-shaped lesion with the urethral meatus at the center (Figure 42–3). The protruding urethral mucosa may become gangrenous if it is not reduced promptly (Kleinjan, 1996). When a young girl has a protruding mass, urethral prolapse must be differentiated from prolapse of a ureterocele (Fernandes et al, 1993; Valerie et al, 1999).

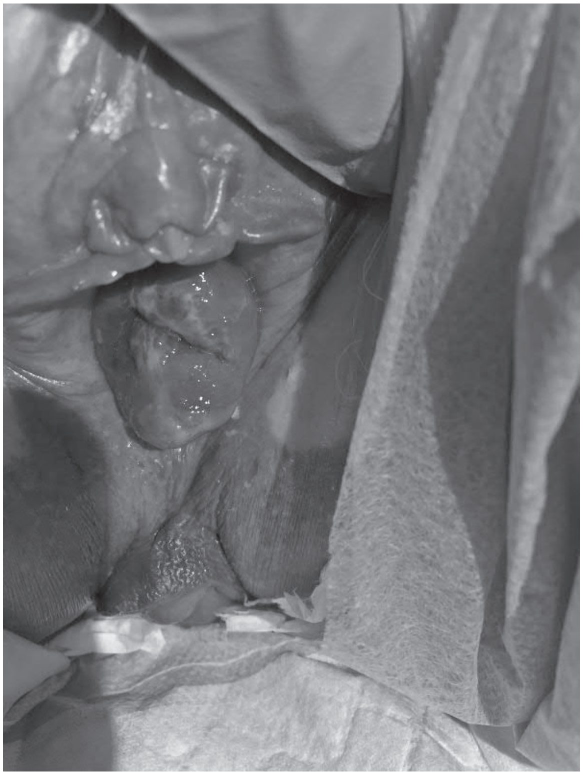
Treatment options include observation, topical creams (estrogen, anti-inflammatory), and sitz baths. Surgical treatments include cauterization, ligation around a Foley catheter, and complete circumferential excision with suture reapproximation of the remaining urethral mucosa to the vaginal wall (Rudin et al, 1997). There is a 67% recurrence rate of nonoperative treatment (Jerkins et al, 1984).

After reduction, cystoscopy should be performed to rule out ureterocele. Recurrences are rare following surgery; the accompanying inflammation probably "fixes" the tissue in place as healing progresses.

URETHROVAGINAL FISTULA

Etiology

In the developing world, urethrovaginal fistulas usually occur as a result of obstructed labor with or without an associated vesicovaginal fistula (VVF) (Elkins, 1994). In the developed world, urethrovaginal fistulas usually have an iatrogenic cause. A common cause is trauma to the urethra or its blood supply in the course of surgical repair of a cystocele or excision of urethral diverticula. Cases of eroded synthetic mesh into the urethra from urethral sling surgery causing urethrovaginal fistulas have been reported (Morton and Hilton, 2009).



▲ **Figure 42–3.** Urethral prolapse. Note the circumferential fleshy protrusion around the urethral meatus. The meatal lumen is the thin transverse "line" in the middle of the mass. Patient also has incidental rectal prolapse.

A neglected pessary used for pelvic organ prolapse can also lead to the formation of fistulas, as can any other foreign body (Hilton and Cromwell, 2012). Other causes may include radiation therapy for pelvic malignancy, trauma/pelvic fracture, and vaginal neoplasms (Flottorp and Inversen, 1960). Finally, pressure necrosis from a chronically indwelling catheter can result in traumatic hypospadias and urethrovaginal fistulas (Andrews and Shah, 1998).

Presentation

Symptoms are usually some degree of urinary incontinence, which can be minimal if the fistula is small up to continuous urine drainage from a large fistula. Distal fistulas past the external sphincter may be completely asymptomatic or associated with a splayed urinary stream.

Diagnosis

Diagnosis can usually be made on physical examination and urethroscopy, but voiding cystourethrography is most useful. An associated VVF will be found in up to 20% of cases; hence a thorough evaluation of the entire lower urinary tract is important (Lee et al, 1988).

Treatment

Treatment is surgical repair and is challenging because of soft-tissue defects and the lack of local viable tissue for a multilayer repair. The quality of the vaginal tissue should be optimized before operation. Excision or removal of any foreign material (eg, synthetic sling) must be performed as in the debridement of any devitalized or inflamed tissue. Often, two or more procedures may be necessary (Webster et al, 1984). A Martius labial fat flap can be used as an interposition layer to augment repair and prevent recurrence of fistula.

Operative Technique

An inverted-U incision is made with the base of the U at the margin of the fistula tract. The vaginal wall flap is developed, exposing the periurethral fascia to the level of the bladder neck or beyond depending on the location of the fistula. The edges of the fistula tract are brought together with absorbable suture for the first layer of closure. The periurethral fascia is reapproximated in a perpendicular suture to the first layer. A Martius flap or other type of flap can be secured over the periurethral fascia. The anterior vaginal wall is then reapproximated. Urinary drainage with a catheter should be used for at least 14 days. There is no consensus regarding the use of a suprapubic catheter alone, or urethral catheter, or both.

URETHRAL DIVERTICULUM

A urethral diverticulum is a urine-filled periurethral cystic structure connected to the urethra through an ostium.

Etiology

The exact origin of urethral diverticulum (UD) is unclear. The vast majority is diagnosed in adult females. The prevalence of diverticulation of the urethral wall is between 1% and 6% (Andersen, 1967; Davis and Robinson, 1970). There are multiple theories regarding the formation of UD. The periurethral glands are thought to be the probable site of origin. Anatomic studies of the female urethra show the periurethral glands located dorsolateral to the urethra, arborizing proximally along the urethra but draining into ducts in the distal third of the urethra (Huffman, 1948). This is supported by the findings that in over 90% of cases, the ostium is located posterolaterally in the midurethra or distal urethra (Lang and Davis 1959). Infection of the periurethral glands seems to be the most generally accepted etiologic factor in most UD cases, with obstruction, suburethral abscess formation, and subsequent rupture of these infected glands into the urethral lumen.

Presentation

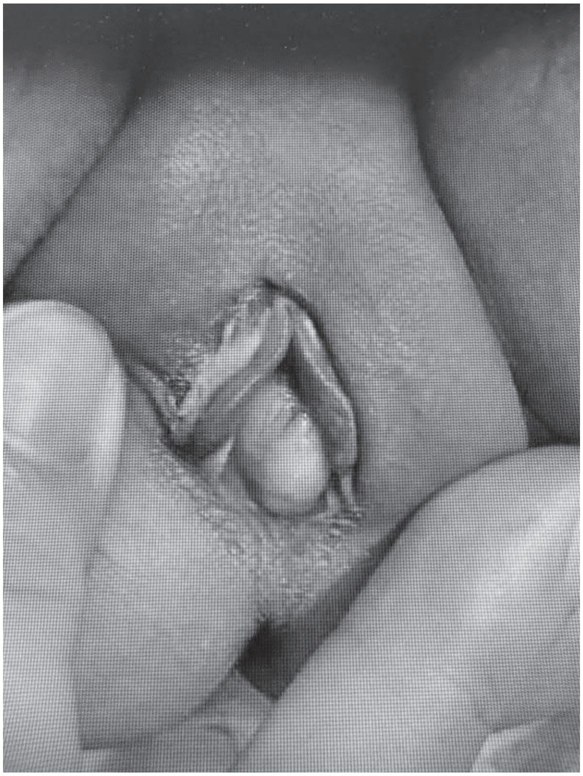
Urethral diverticula are usually associated with recurrent attacks of urinary infection, irritative voiding symptoms (frequency, urgency), and pain (Davis and TeLinde, 1958; Leach et al, 1986). The classic mnemonic is the three "Ds": dysuria, dyspareunia, and dribbling, but this triad of symptoms is rarely seen. Other complaints include vaginal mass, hematuria, vaginal or urethral discharge, obstructive symptoms, and incontinence. Gentle compression of the vaginal "bulge" may express urine or purulent discharge per urethral meatus. Up to 20% of patients diagnosed with UD may be completely asymptomatic. The size of the diverticulum does not correlate with symptoms, and symptoms may wax and wane.

Evaluation and Diagnosis

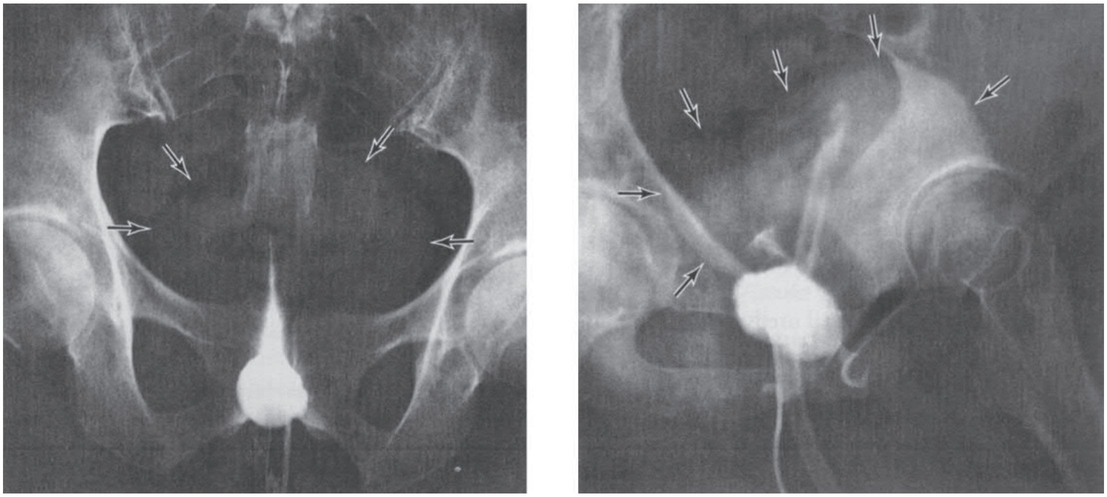
A thorough history is essential, including past surgeries such as any pelvic surgery, urethral sling, or injection of urethral bulking agents. In addition, the presence of incontinence and sexual function and dyspareunia should be recorded because vaginal reconstructive surgery may affect these symptoms favorably or adversely.

The diagnosis is usually made on feeling a rounded cystic mass in the anterior wall of the vagina (ventral to the urethra) that leaks pus from the urethral orifice with gentle "milking" of the urethra. However, UD can be located anterior to the urethra, extending around the urethra or proximally toward the bladder neck. Diverticula are at times multiple or lobulated. A few cases of carcinoma in such diverticula have been reported (Kato et al, 1998; Marshall, 1977; Nakamura et al, 1995). A hard mass on palpation may denote calculus that has formed in the urethral diverticulum (Figure 42–4).

Differential diagnoses include Skene gland cysts or abscesses, vaginal masses (leiomyoma), Gartner duct cysts, or periurethral bulking agents (Figure 42–5).



▲ **Figure 42–5.** Neonatal Skene gland in a 3-week-old girl. Introitus is posterior and right lateral to the lesion. Daily sitz baths were started. The lesion regressed.



▲ **Figure 42–4.** Urethral diverticulum containing stone. ***Left:*** Plain film showing stone. *Arrows* outline bladder. ***Right:*** Diverticulum filled with radiopaque fluid instilled through ureteral catheter. Bladder outlined by *arrows*.

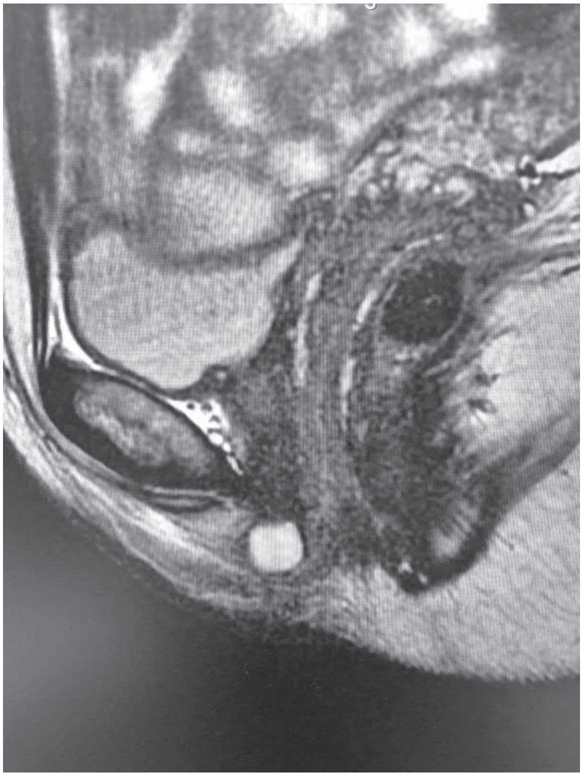
Cystourethroscopy may reveal the urethral opening, although the openings are often very difficult to locate. The ostium is most often along the 4–8 o'clock position at the level of the middle to distal urethra. Cystoscopy is also used to evaluate for other causes of the patient's lower urinary tract symptoms.

There is no single gold standard imaging study for UD. Current available techniques include double-balloon urethrography, voiding cystourethrography (VCUG), ultrasonography, and magnetic resonance imaging (MRI).

The two most common office procedures for elucidating the UD are as follows:

1. **Positive-pressure VCUG + cystoscopy**: Empty the diverticulum manually. Through a catheter, instill 5 mL of indigo carmine and 60 mL of contrast medium into the bladder. Remove the catheter, and have the patient begin to void. Occlude the meatus with a finger. This maneuver usually causes the diverticulum to fill with the test solution. Take appropriate x-rays, and perform urethroscopy to look for leakage of blue dye from the ostium of the diverticulum. A normal VCUG may push some contrast into the UD, and imaging will show the diverticulum even without blocking the urinary stream.
2. **Double-balloon positive-pressure urethrography**: Insert a Davis–TeLinde catheter or Trattner catheter. This resembles a Foley catheter, but there is a second movable balloon that remains distal to the meatus. Pass the catheter to the bladder and inflate the proximal balloon. While pulling on the catheter gently and sealing the bladder neck, slide the second balloon against the urinary meatus and inflate it. Then inject contrast medium into the catheter. The radiopaque fluid will exit from the catheter through a side hole between the balloons and will fill the urethra and diverticulum, after which x-rays can be exposed. This provides excellent images of the urethra and UD. The advantage is that this technique is not dependent on the patient voiding during the study. However, the double-balloon catheter is highly specialized and must be stocked specially.

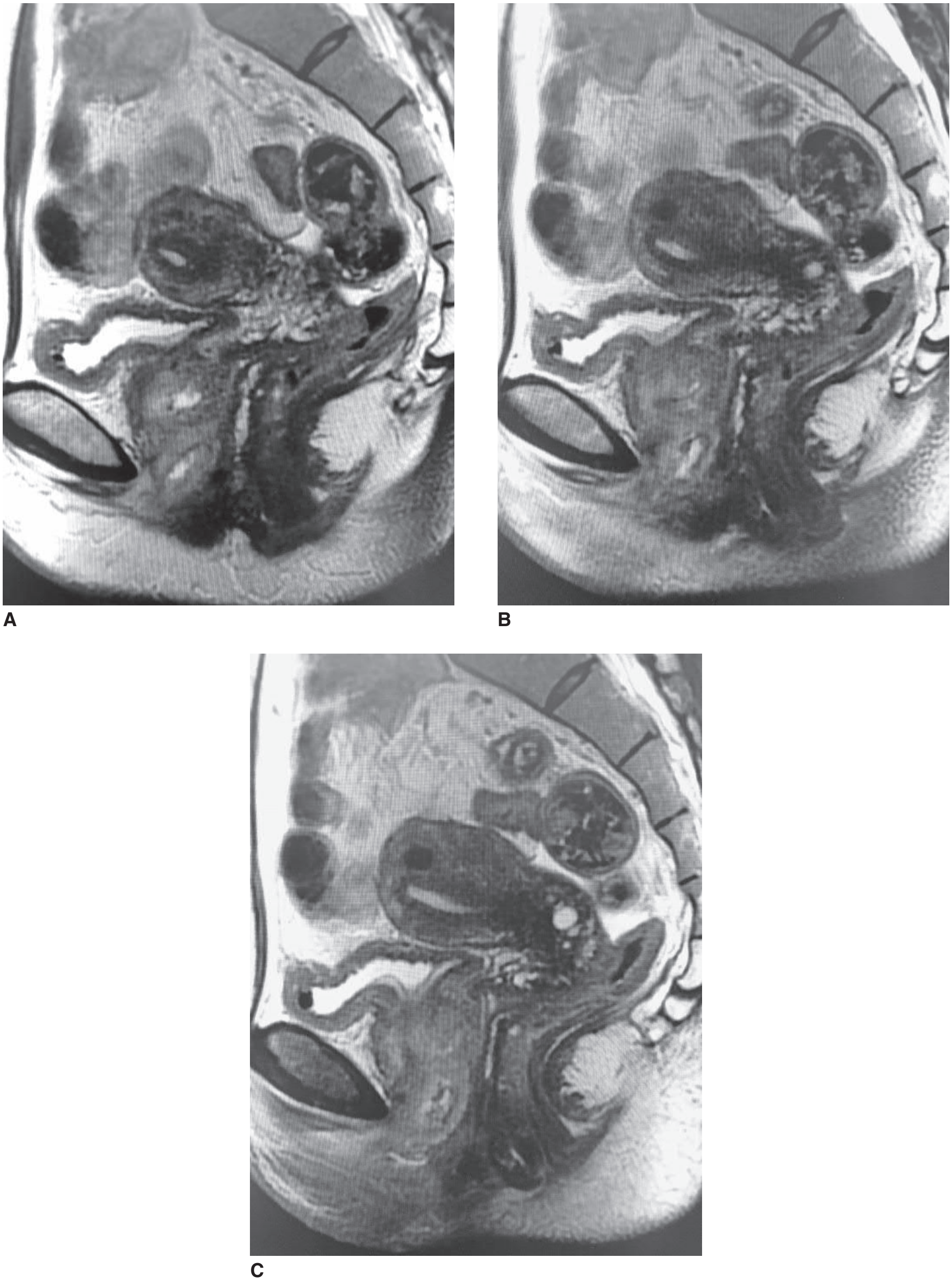
Transvaginal ultrasonography (Baert, 1992; Mouritsen and Bernstein, 1996; Siegel et al, 1998; Vargas-Serrano et al, 1997) or pelvic MRI (Chaudhari et al, 2010; Debaere et al, 1995; Kim et al, 1993) can be helpful in diagnosis; MRI is reported to be much more sensitive in detecting diverticula than double-balloon urethrography (Neitlich et al, 1998), especially when an endoluminal coil is placed in the vagina to enhance the periurethral imaging (Dwarkasing et al, 2011). MRI is useful in assessing urethral diverticula, but there are limitations. A study by Chung et al (2010) revealed 24% discrepancy between MRI and surgical findings. Examples include misdiagnosis of the diverticulum as Bartholin's cyst, a sterile abscess incorrectly diagnosed as a diverticulum, and missed detection of cancer within the diverticulum (Figures 42–6 and 42–7).



▲ **Figure 42–6.** Sagittal image of a pelvic MRI of a simple distal urethral diverticulum. The lesion is brighter white than the urine in the bladder at the most distal aspect of the urethra.

Surgical Technique

The patient is placed in lithotomy position. A Foley catheter is placed. A weighted vaginal speculum is used for exposure. An inverted-U incision is made with the base of the U at the distal urethra. The vaginal wall flap is developed, exposing the periurethral fascia to the level of the bladder neck or beyond, depending on the location of the diverticulum. Avoid inadvertent entry into the UD. Preservation of a distinct periurethral fascia will allow use of this procedure as the interposition layer to prevent recurrence and urethrovaginal fistula formation. Usually a transverse incision is made through the periurethral fascia, and this layer is developed. The UD sac is then grasped and dissected down to the urethra. Often it is necessary at this point to enter the diverticulum to facilitate dissection from the surrounding tissue. If it is not possible or safe to remove all the walls of the diverticulum as the separation medially from the urethra can be very thin, every effort should be made to remove the mucosalized surface to prevent recurrence. If the ostium to the urethra is not easily appreciated, lacrimal probes can be used to gently probe the



▲ **Figure 42–7.** ***A–C:*** Sagittal images of a pelvic MRI of a complex urethral diverticulum. This lesion engulfs the entire urethra as compared to Figure 42–6. This was mistaken for anterior vaginal wall prolapse on physical examination. The heterogeneous nature of the lesion was very concerning for malignancy. Biopsies were performed that showed squamous metaplasia with acute inflammation, edema, and fibrosis. It was negative for dysplasia or malignancy.

"pits" in the mucosa. The Foley catheter is often seen through the operative site following excision of the UD. This urethral defect is reconstructed in a watertight fashion with absorbable sutures. Complex UD that extend circumferentially around the urethra will require segmental resection and complex reconstruction (Rovner and Wein, 2003). The periurethral flaps are then reapproximated in a perpendicular orientation to the urethral closure. Care is taken to eliminate all dead space. The anterior vaginal wall flap is then reapproximated. A vaginal pack can be used for hemostasis control.

A suprapubic cystostomy or urethral catheter should be left in place for 2–3 weeks following surgical excision of the diverticulum.

The outcome is usually good unless the diverticulum is so situated that its excision injures the external urinary sphincter mechanism. In a few cases, urethrovaginal fistula have developed. If the fistula does not close with adequate drainage, surgical repair will be necessary 2–3 months later.

URETHRAL STRICTURE

True anatomical stricture of the adult female urethra is not common. Functional urethral obstruction is more common, due to pelvic floor dysfunction. It may be congenital or acquired. The trauma of intercourse and especially of childbirth may lead to periurethral fibrosis with contracture, or the stricture may be caused by the surgeon during vaginal repair. It may develop secondary to acute or chronic urethritis. Pelvic irradiation is another etiologic factor.

Persistent hesitancy in initiating urination and a slow urinary stream are the principal symptoms of stricture. Burning, frequency, nocturia, and urethral pain may occur from secondary urethritis or cystitis. If secondary infection of the bladder is present, white blood cells and bacteria will be found in the urine. A fairly large catheter (22F) may pass to the bladder only with difficulty. Urethroscopy may demonstrate the point of narrowness and disclose evidence of urethritis. Cystoscopy often reveals trabeculation (hypertrophy) of the bladder wall.

Chronic cystitis may cause similar symptoms, but urinalysis reveals evidence of infection. Cancer of the urethra can cause progressive narrowing of the urethra, but induration and infiltration of the urethra are found on vaginal examination. Panendoscopy with biopsy establishes the diagnosis. A bladder tumor involving the bladder neck causes hesitancy and impairment of the urinary stream. Cystoscopy and biopsy are definitive. Chronic urethritis commonly accompanies urethral stenosis; either may be primary. Recurrent or chronic cystitis is often secondary to stenosis.

Treatment consists of gradual urethral dilatation (up to 36Fr) at weekly intervals. Slight overstretching is necessary, since some contracture will occur after therapy is discontinued. Measures to combat urethritis and cystitis also must be employed. Internal urethrotomy has its proponents (Essenhigh, 1968). With proper overdilation of the urethra and specific therapy of the urethritis that is usually present, the prognosis is good. Formal urethroplasty can be performed with high success rates in cases that do not respond to urethral dilations (Onol, 2011).

BIBLIOGRAPHY

Distal Urethral Stenosis

Amer MI et al: Congenital urethrovaginal fistula with transverse vaginal septum. J Obstet Gynaecol Res. 2016;42(8):1042–1045.

Immergut MA, Gilbert EC: Internal urethrotomy in recurring urinary infections in girls. J Urol 1973;109:126.

Kaplan GW et al: A blind comparison of dilatation, urethrotomy and medication alone in the treatment of urinary tract infection in girls. J Urol 1973;109:917.

Kondo A et al: Functional obstruction of the female urethra: Relevance to refractory bed wetting and recurrent urinary tract infection. Neurourol Urodyn 1994;13(5):541–546.

Lyon RP, Marshall S: Urinary tract infections and difficult urination in girls: Long-term follow-up. J Urol 1971;105:314.

Lyon RP, Tanagho EA. Distal Urethral Stenosis In Little Girls. J Urol 1965;93:379–388.

Malin G et al: Congenital lower urinary tract obstruction: A population-based epidemiological study. Br J Obstet Gynecol 2012;119(12):1455–1464.

Smith DR: Critique on the concept of vesical neck obstruction in children. JAMA 1969;207:1686.

Tanagho EA et al: Spastic external sphincter and urinary tract infection in girls. Br J Urol 1971;43:69.

Labial Fusion (Synechia Vulvae)

Adekunle AO et al: Female genital mutilation—postcircumcision vulval complications in Nigerians. J Obstet Gynaecol 1999;19:632.

Aribarg A: Topical oestrogen therapy for labial adhesions in children. Br J Obstet Gynaecol 1975;82:424.

Christensen EH, Oster J: Adhesions of labia minora (synechia vulvae) in childhood: A review and report of fourteen cases. Acta Paediatr Scand 1971;60:709.

Kumar RK et al: Labial adhesions in pubertal girls. Arch Gynecol Obstet 2006;273:243.

Leung AK et al: Treatment of labial fusion with topical estrogen therapy. Clin Pediatr (Philadelphia) 2005;44:245.

Acute Urethritis

Bass HN: "Bubble bath" as an irritant to the urinary tract of children. Clin Pediatr 1968;7:174.

Marshall S: The effect of bubble bath on the urinary tract. J Urol 1965;93:112.

Simms I, Stephenson JM: Pelvic inflammatory disease epidemiology: What do we know and what do we need to know? Sex Transm Infect 2000;76:80.

Chronic Urethritis

Bruce AW et al: Recurrent urethritis in women. Can Med Assoc J 1973;108:973.

Farrar DJ et al: An evaluation of Otis urethrotomy in female patients with recurrent urinary tract infections: A review after 6 years. Br J Urol 1980;52:68.

Immergut MA, Gilbert EC. Internal urethrotomy in recurring urinary infection in girls. J Urol 1973;109(1):126–127.

Krieger JN et al: Evaluation of chronic urethritis: Defining the role for endoscopic procedures. Arch Intern Med 1988;148:703.

Marshall S et al: Nonspecific urethritis in females. Calif Med 1970;112:9.

Simpson T et al: Vaginal douching among adolescent and young women: More challenges than progress. J Pediatr Adolesc Gynecol 2004;17:249.

Atrophic Urethritis

Eriksen B: A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 1999;180(5):1072–1079.

Johnston SL et al: The detection and management of vaginal atrophy. J Obstet Gynaecol Can 2004;26:503.

Quinlivan LG: The treatment of senile vaginitis with low doses of synthetic estrogens. Am J Obstet Gynecol 1965;92:172.

Raz R, Stamm WE: A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. New Engl J Med 1993;329:753.

Smith P: Age changes in the female urethra. Br J Urol 1972;44:667.

Sturdee DW, Panay N: Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 2010;13:509.

Urethral Caruncle

Atalay AC et al: Non-Hodgkin's lymphoma of the female urethra presenting as a caruncle. Int Urol Nephrol 1998;30(5):609–610.

Indudhara R et al: Urethral tuberculosis. Urol Int 1992;48(4): 436–438.

Lee WH et al: The aetiology of postmenopausal bleeding—a study of 163 consecutive cases in Singapore. Singapore Med J 1995;36:164.

Lopez JI, et al: Primary malignant melanoma mimicking urethral caruncle. Case report. Scand J Urol Nephrol 1993;27(1):125–126.

Neilson D et al: Squamous intra-epithelial neoplasia presenting as a urethral caruncle. Br J Urol 1989;64:200.

Willett GD1, Lack EE: Periurethral colonic-type polyp simulating urethral caruncle. A case report. J Reprod Med 1990;35(11):1017–1078.

Young RH et al: Urethral caruncle with atypical stromal cells simulating lymphoma or sarcoma—a distinctive pseudoneoplastic lesion of females. A report of six cases. Am J Surg Pathol 1996;20:1190.

Prolapse of the Urethra

Desai SR, Cohen RC: Urethral prolapse in a premenarchal girl: Case report and literature review. Austral NZ J Surg 1997;67(9):660–662.

Devine PC, Kessel HC: Surgical correction of urethral prolapse. J Urol 1980;123:856.

Fernandes ET et al: Urethral prolapse in children. Urology 1993;41:240.

Jerkins GR et al: Treatment of girls with urethral prolapse. J Urol 1984;132(4):732–733.

Kleinjan JH, Vos P: Strangulated urethral prolapse. Urology 1996;47:599.

Lowe FC et al: Urethral prolapse in children: Insights into etiology and management. J Urol 1986;135(1):100–103.

Rudin JE et al: Prolapse of urethral mucosa in white female children: Experience with 58 cases. J Pediatr Surg 1997;32(3):423–425.

Valerie E et al: Diagnosis and treatment of urethral prolapse in children. Urology 1999;54:1082.

Urethrovaginal Fistula

Andrews HO, Shah PJ: Surgical management of urethral damage in neurologically impaired female patients with chronic indwelling catheters. Br J Urol 1998;82(6):820–824.

Creatsas G et al: Reconstruction of urethrovaginal fistula and vaginal atresia in an adolescent girl after an abdominoperineal-vaginal pull-through procedure. Fertil Steril 1997;68:556.

Elkins TE: Surgery for the obstetric vesicovaginal fistula: A review of 100 operations in 82 patients. Am J Obstet Gynecol 1994;170:1108.

Flottorp J, Inversen S: [Vesicovaginal and urethrovaginal fistulas treated at the Norwegian Radium Hospital 1940-1952 and in the gynecological department of the Rikshospitalet 1953-1959.] Tidsskr Nor Laegeforen 1960;80:597–599.

Hilton P, Cromwell DA: The risk of vesicovaginal and urethrovaginal fistula after hysterectomy performed in the English National Health Service—a retrospective cohort study examining patterns of care between 2000 and 2008. Br J Obstet Gynecol 2012;119(12):1447–1454.

Lee RA et al: Current status of genitourinary fistula. Obstet Gynecol 1988;72(3 Pt 1):313–319(review).

Morton HC, Hilton P: Urethral injury associated with minimally invasive mid-urethral sling procedures for the treatment of stress urinary incontinence: A case series and systematic literature search. B J Obstet Gynecol 2009;116(8):1120–1126.

Webster GD et al: Urethrovaginal fistula: A review of the surgical management. J Urol 1984;132:460.

Urethral Diverticulum

Andersen MJ: The incidence of diverticula in the female urethra. J Urol 1967;98:96.

Baert L et al: Endovaginal sonography: New diagnostic approach for urethral diverticula. J Urol 1992;147:464.

Chaudhari VV et al: MR imaging and US of female urethral and periurethral disease. Radiographics 2010;30:1857.

Chung DE et al: Urethral diverticula in women: Discrepancies between magnetic resonance imaging and surgical findings. J Urol 2010;183:2265.

Davis BL, Robinson DG: Diverticula of the female urethra: Assay of 120 cases. J Urol 1970;104:850.

Davis HJ, TeLinde RW. Urethral diverticula: an assay of 121 cases. J Urol 1958;80(1):34–39.

Debaere C et al: MR imaging of a diverticulum in a female urethra. J Belge Radiol 1995;78:345.

Dwarkasing RS et al: MRI evaluation of urethral diverticula and differential diagnosis in symptomatic women. Am J Roentgenol 2011;197:676.

Elik M: Diverticulum of the female urethra: A new method of ablation. J Urol 1957;77:243.

Huffman JW: The detailed anatomy of the para-urethral ducts in the adult human female. Am J Obstet Gynecol 1948;55(1):86–101.

Kato H et al: Carcinoembryonic antigen positive adenocarcinoma of a female urethral diverticulum: Case report and review of the literature. Int J Urol 1998;5:291.

Kim B et al: Diagnosis of urethral diverticula in women: Value of MR imaging. Am J Roentgenol 1993;161:809.

Lang EK, Davis HJ: Positive pressure urethrography: A roentgenographic diagnostic method for urethral diverticula in the female. Radiology 1959;72(3):401–405.

Leach GE, Schmidbauer CP, Hadley HR et al. Surgical treatment of female urethral diverticulum. Semin Urol 1986;4(1):33–42.

Marshall S, Hirsch K: Carcinoma within urethral diverticula. Urology 1977;10:161.

Mouritsen L, Bernstein I: Vaginal ultrasonography: A diagnostic tool for urethral diverticulum. Acta Obstet Gynecol Scand 1996;75:188.

Nakamura Y et al: A case of adenocarcinoma arising within a urethral diverticulum diagnosed only by the surgical specimen. Gynecol Obstet Investig 1995;40:69.

Neitlich JD et al: Detection of urethral diverticula in women: Comparison of a high resolution fast spin echo technique with double balloon urethrography. J Urol 1998;159:408.

Presman D et al: Calculus formation within a diverticulum of the female urethra. J Urol 1964;91:376.

Rovner ES, Wein AJ: Diagnosis and reconstruction of the dorsal or circumferential urethral diverticulum. J Urol. 2003;170(1):82–86; discussion 86.

Siegel CL et al: Sonography of the female urethra. Am J Roentgenol 1998;170:1269.

Vargas-Serrano B et al: Transrectal ultrasonography in the diagnosis of urethral diverticula in women. J Clin Ultrasound 1997;25:21.

Urethral Stricture

Essenhigh DM et al: A study of the bladder outlet in lower urinary tract infections in women. Br J Urol 1968;40:268.

Onol FF et al: Techniques and results of urethroplasty for female urethral strictures: Our experience with 17 patients. Urology 2011;77:1318.

Disorders of Sex Development

43

Laurence S. Baskin, MD

What defines our sexuality is a complex interaction between our genetic makeup, environmental stimulus, and cultural influences. The origins of our sexuality occur at the time of conception when the genetic material from two sources of the opposite sex coalesces into a new individual. From that moment, sexual differentiation occurs by a highly organized process. Sex chromosomes and autosomes dictate the development of gonads; the gonads, in turn, produce hormones, which then direct the development of the internal and external genitalia. Disorders of sex development (DSD) or differentiation arise from abnormalities in chromosomes, gonadal development, or hormonal production/activity.

Patients with DSD become apparent (1) during the newborn period as having atypical genitalia or a discordant phenotypic from the genotype found at the time of amniocentesis, (2) as having inappropriate pubertal development, (3) as having delayed pubertal development, or (4) later in life as having infertility.

NORMAL SEXUAL DIFFERENTIATION

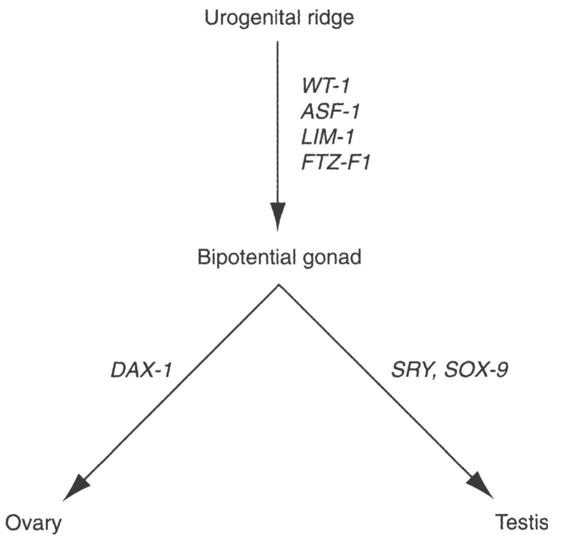
Chromosomal Sex

The genetic material necessary for the development of the male phenotype is normally located on the short arm of the Y chromosome (Wilson et al, 1981). The critical gene or sex-determining region on the Y chromosome is known as the **SRY region**. The gene products of the SRY genetic cascade direct the development of the testis by interacting with multiple other genes such as testis-determining factor and *SOX-9* (Conte and Grumbach, 2007). Genetic information that is known to be necessary for male and female development beyond gonadal differentiation is located on the X chromosome and on the autosomes.

Gonadal Differentiation

The gonads develop from the urogenital ridges (Figure 43–1), which are formed during week 4 of gestation by the proliferation of the coelomic epithelium and condensation of the underlying mesenchyme along the mesonephros. The germ cells, located in the endoderm of the yolk sac, migrate to the genital ridges. At the early stage of development, the gonad is bipotential, capable of forming into either a testis or an ovary. During gestation weeks 6–7 at least four different genes, Wilms' tumor suppressor gene (*WT-1*), Fushi–Tarza factor 1 (*FTZ-F1*), steroidogenic factor 1 (*SF-1*), and *LIM-1*, induce the development of the testis. The primordial germ cells differentiate into the Sertoli cells and associated Leydig cells, which aggregate into spermatogenic cords. Loose mesenchymal tissue condenses into a thick layer, the tunica albuginea, which surrounds the testis and separates its connection with the coelomic epithelium, thereby preventing further migration of mesonephric cells into the testis.

Classic teaching is that the female phenotype is the default developmental pathway in the absence of the SRY cascade. It is now known that at least one gene, dosage-sensitive sex reversal (*DAX-1*), is essential for ovarian development. *DAX-1* is located on the short arm of the X chromosome. The gene products of *SRY* and *DAX-1* compete to stimulate the steroidogenic acute regulatory protein (StAR). The StAR protein is the first step in steroidogenesis, facilitating the conversion of cholesterol to pregnenolone. In the normal XY male, *SRY* overwhelms the one functional *DAX-1* gene, stimulating testicular development and subsequent testosterone production. In the normal XX female, two *DAX-1* genes are present without the competitive *SRY*, downregulating StAR, thus inhibiting testicular development, which results in ovarian development. In the fetal ovaries, the germ cells differentiate and are arrested in the last phase of meiotic prophase, forming the oocytes. The cells in the genital ridges



▲ **Figure 43–1.** Sex-determining genes involved in testes and ovarian development.

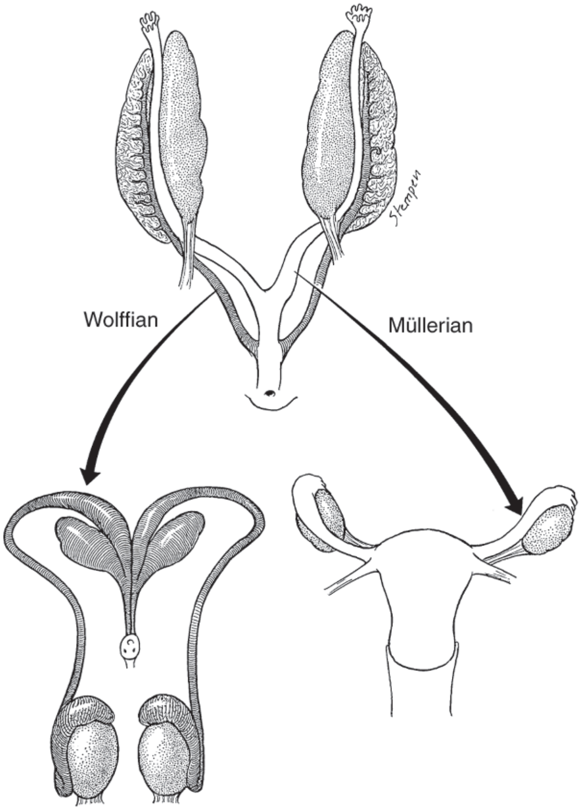
develop into granulosa cells, which surround the oocytes and complete the formation of the ovaries.

Hormones

At 3.5 weeks' gestation, the Wolffian system appears as two longitudinal ducts connecting cranially to the mesonephros and caudally draining into the urogenital sinus (Figure 43–2). At approximately the sixth week of gestation, the Müllerian duct develops as an evagination in the coelomic epithelium just lateral to the Wolffian duct.

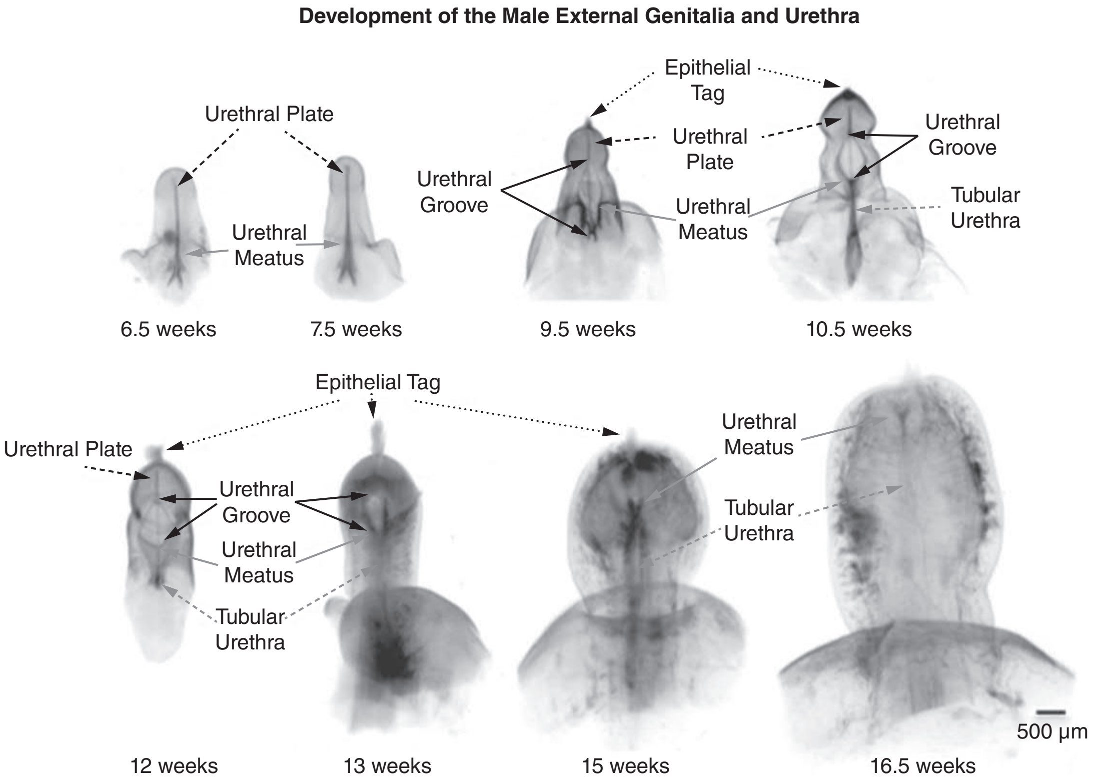
During gestation weeks 8–9, Sertoli cells of the fetal testis secrete a glycoprotein, Müllerian-inhibiting substance (MIS), or anti-Müllerian hormone. This protein induces the regression of the Müllerian ducts through the dissolution of the basement membrane and condensation of mesenchymal cells around the Müllerian duct. Because MIS acts locally, Müllerian duct regression occurs only on the ipsilateral side of the fetal testis producing this hormone. MIS also induces the formation of seminiferous tubules and further differentiation of the testis. At gestation week 9 or 10, the Leydig cells appear in the testis and begin to synthesize testosterone. This hormone transforms the Wolffian duct into the male genital tract, which is completed by the end of gestation week 11.

Beginning in gestation week 9, testosterone also induces the development of the external genitalia (Figure 43–3) from the genital tubercle, urogenital sinus, and genital swellings (Jirasek et al, 1968). At the molecular level, testosterone is converted to 5α-dihydrotestosterone (DHT) by the microsomal enzyme, type 2 5α-reductase, for complete differentiation of the penis with a male-type urethra and glans (Wilson et al, 1993). Testosterone dissociates from its carrier proteins in the plasma and enters cells via passive diffusion. Once in the cell, testosterone binds to the androgen receptor (AR) and induces changes in conformation, protecting it from degradation by proteolytic enzymes. This conformational change is also required for AR dimerization, DNA binding, and transcriptional activation, all necessary for testosterone to be expressed. Androgen binding also displaces heat-shock proteins, possibly relieving constraints on receptor dimerization or DNA binding. After entering the nucleus, the AR complex then binds androgen response element DNA regulatory sequences within the androgen responsive genes and activates them. DHT also binds the AR, with enhanced androgenic activity, in part because of its slow dissociation rate from the AR.



▲ **Figure 43–2.** Schematic representation of male (Wolffian) and female (Müllerian) internal and external genital development from common origin.

Then DHT binds to nuclear receptors, forming a complex that regulates the transformation of these tissues into the glans penis, penile and cavernous urethra, Cowper's glands, prostate, and scrotum. Between gestation weeks 28 and 37, testicular descent into the scrotum begins. While the



▲ **Figure 43–3.** Differentiation of the fetal male external genitalia and urethra from the indifferent stage to full differentiation (6.5–16 weeks) depicted by optical projection tomography. Note the progression of the urethral meatus (*green arrows*) from the scrotal folds at 6.5 weeks to a terminal position on the glans at 16.5 weeks. The wide open urethral groove (*red arrows*) is best seen from 9.5 to 13 weeks with clear progression of a proximal-to-distal fusion of the edges of urethral groove to form the tubular urethra (*yellow arrows*). At 13 weeks the urethra groove is within the glans penis with the tubular urethra completely formed within the shaft of the penis consistent with the endodermal theory of urethral development. No evidence of ectodermal intrusion is noted in any of the specimens.

mechanism of this process is not completely understood, it is clearly androgen-dependent.

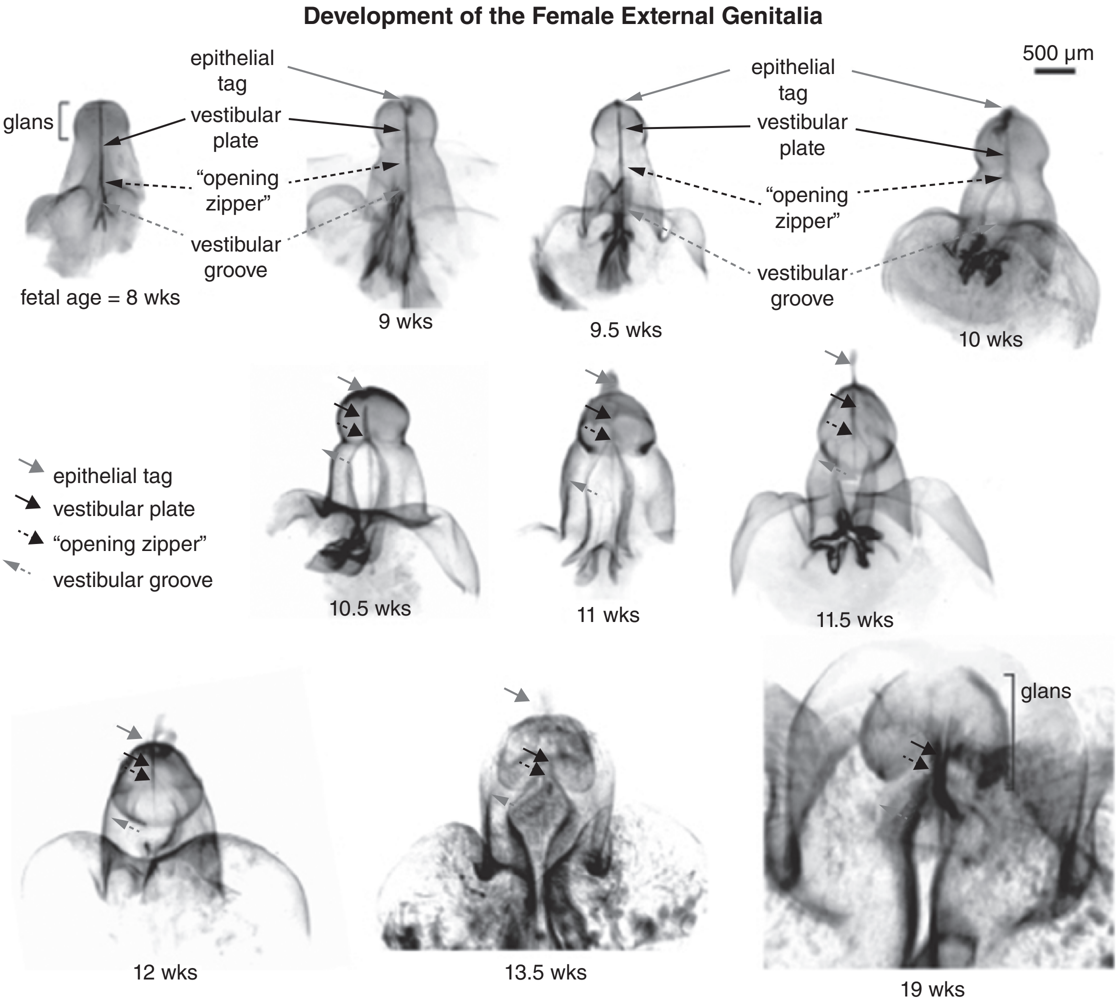
▶ Development of the Female Genitalia

The female internal genitalia develop from the Müllerian ducts. Without the hormones produced by the testis, the Wolffian ducts regress at gestation week 9. At the same time, the Müllerian ducts begin to differentiate; the cranial portions form the fallopian tubes, while the caudal portions fuse to form the uterus, cervix, and the upper portion of the vagina. Concurrently, the external genitalia, defined as the lower portion of the vagina, the vestibule, the Bartholin and Skene glands, the clitoris, and labia minora and majora, develop from the urogenital sinus and genital tubercles. Like the testis, the ovary undergoes a partial transabdominal descent. However, transinguinal descent of the ovary does not occur, leaving the ovaries just below the rim of the true pelvis. The role of estrogen in the differentiation of the female phenotype is unclear.

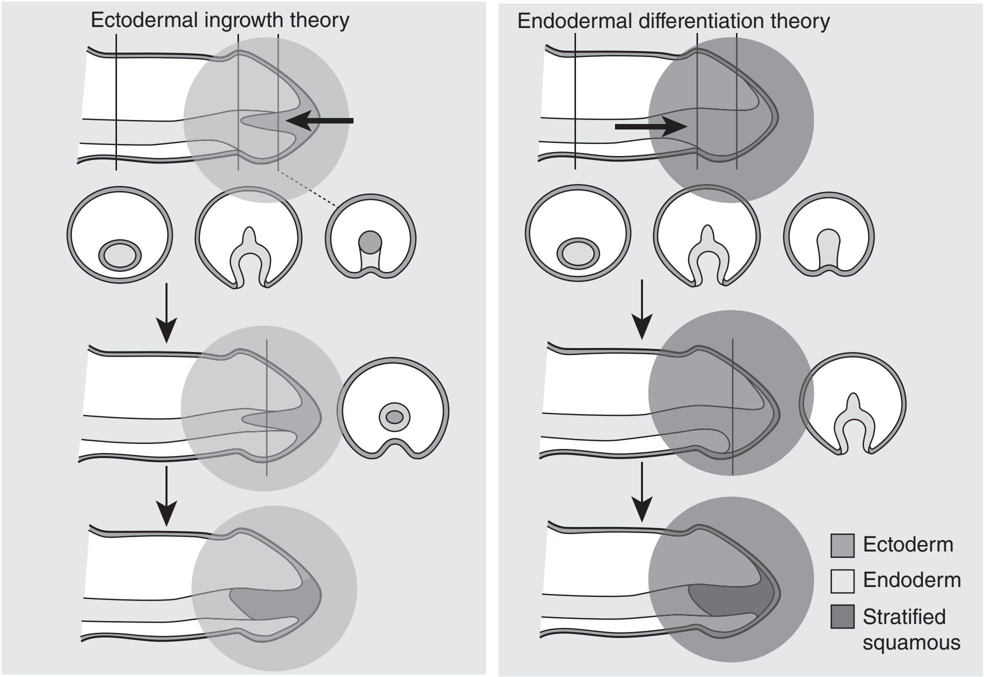
▶ Development of the Male External Genitalia

Formation of the external male genitalia is a complex developmental process involving the SRY genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. By the end of the first month of gestation, the hindgut and the future urogenital system reach the ventral surface of the embryo at the cloacal membrane. The urorectal septum divides the cloacal membrane into a posterior, or anal, half and an anterior half, the urogenital membrane. Three protuberances appear around the latter. The most cephalad is the genital tubercle. The other two, the genital swellings, flank the urogenital membrane on each side. Up to gestation weeks 7–8 the male and female genitalia are essentially indistinguishable (Figures 43–3 and 42–4). Under the influence of testosterone in response to a surge of luteinizing hormone from the pituitary, masculinization of the external genitalia takes place. One of the first signs of masculinization is an increase in the distance between the anus and the genital structures, followed by elongation of the phallus, formation of the penile urethra from the urethral groove, and development of the prepuce (Figure 43–3).

At 8 weeks' gestation, the external genitalia remain in the indifferent stage. The urethral forms by a two-step process that involves canalization (opening zipper) that is androgen-independent and also occurs during development of the female external genitalia (Figure 43–4) (Li et al, 2015; Overland et al, 2016). The second step is the androgen-dependent fusion process (closing zipper) that occurs only in the male. The urethral groove on the ventral surface of the phallus is between the paired urethral folds. The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds. As development progresses, the ectodermal edges of the urethral groove begin to fuse to form the median raphe (Figure 43–3). By gestation weeks 11–12, the coronal sulcus separates the glans from the shaft of the penis. By 16 weeks' gestation, the urethral folds have



▲ **Figure 43–4.** Differentiation of the fetal female external genitalia from the indifferent stage to full differentiation (8–19 weeks' gestation). Note the opening zipper that facilitates opening of the vestibular plate to form the vestibular groove. Also note the lack of closing zipper, with the vestibular groove remaining open. Respective arrows denote the epithelial tag, vestibular plate, opening zipper, and vestibular groove.



▲ **Figure 43–5.** Theories of human penile urethral development. The ectodermal ingrowth theory as described in older textbooks of embryology postulates that the glandular urethra is formed by ingrowth of epidermis. More recent data support the formation of the entire urethra via endodermal differentiation alone.

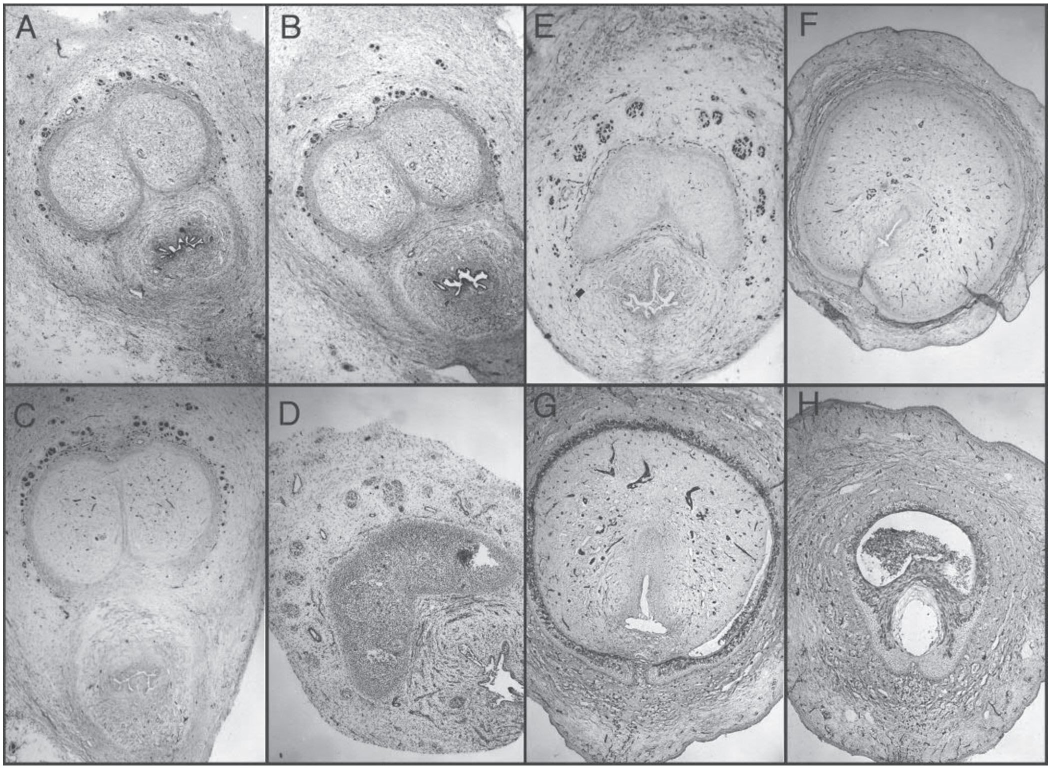
completely fused in the midline on the ventrum of the penile shaft (Figure 43–3). During normal male development there is a progression from normal ventral penile curvature, or chordee, that resolves by the 19th week (Figure 43–3).

The glandular urethra, which consists of a squamous epithelium-lined tube different from the urothelium-lined anterior urethra, also completes its formation during this period. Evidence suggests two possible explanations for glandular urethral formation (Figure 43–5):

1. **Modern:** Endodermal cellular differentiation where the glandular urethra forms by an extension of urogenital sinus epithelium that undergoes transdifferentiation versus (Kurzrock et al, 1999).
2. **Historic:** Primary intrusion of the ectodermal tissue from the skin of the glans penis. Cross-sectional histologic analysis at 24 weeks' gestation reveals complete penile development (Figure 43–6). Note the extensive neuronal innervation just above the tunica of the corporeal bodies. Three-dimensional reconstruction of the fetal male penis illustrates the extensive neuronal distribution (Figure 43–7). Note the nerve density in the glans (Figure 43–7E,F).

Anatomical and immunohistochemical studies advocate the new theory of endodermal differentiation, which shows that epithelium of the entire urethra is of urogenital sinus origin. The entire male urethra, including the glandular urethra, is formed by dorsal growth of the urethral plate into the genital tubercle and ventral growth and fusion of the urethral folds. Under proper mesenchymal induction, urothelium can differentiate into a stratified squamous phenotype with characteristic keratin staining, thereby explaining the cell type of the glans penis.

The future prepuce is forming at the same time as the urethra and is dependent on normal urethral development. At about 8 weeks' gestation, low preputial folds appear on both sides of the penile shaft, which join dorsally to form a flat ridge at the proximal edge of the corona. The ridge does not entirely encircle the glans because it is blocked on the ventrum by incomplete development of the glandular urethra. Thus, the preputial fold is transported distally by active growth of the mesenchyme between it and the glandular lamella. The process continues until the preputial fold (foreskin), covers the entire glans, forming a midline seam (Figure 43–3, ages 13–16 weeks gestation). The fusion is usually present at birth, but subsequent desquamation of the epithelial fusion allows the prepuce to retract. If the genital folds fail to fuse, the preputial tissues do not form ventrally; consequently, in hypospadias, preputial tissue is absent on the ventrum, and excessive dorsally.



▲ **Figure 43–6.** Normal human fetal penis, 24 weeks *(**A–H**)*. Transverse histologic sections show immunohistochemical localization with the neuronal marker S-100 (25×) (*dark brown staining*). Note localization of S-100 nerve marker (*dark staining*) completely surrounding the cavernous bodies up to the junction with the urethral spongiosum along the penile shaft except at the 12 o'clock position *(**A–D**)*. On the proximal penis at the point where the corporeal bodies split into two *(**E**)* and continue in a lateral fashion inferior and adjacent to the pubic rami, the nerves localize to an imaginary triangular area at the 11 o'clock and 1 o'clock positions. At this point *(**E**)*, the nerves reach their farthest vertical distance from the corporeal body (approximately one-half the diameter of the corporeal body) and continue *(**F–G**)* in a tighter formation at the 11 o'clock and 1 o'clock positions well away from the urethra.

▶ Disorders of Sexual Differentiation

Disorders of abnormal sexual differentiation may be divided into the following three categories.

A. Disorders of Chromosomal Sex

This result from abnormalities in the number or structure of the sex chromosomes. These abnormalities may arise from nondisjunction, deletion, breakage, rearrangement, or translocation of genetic material on these chromosomes. These disorders are summarized in Table 43–1.

B. Disorders of Gonadal Sex

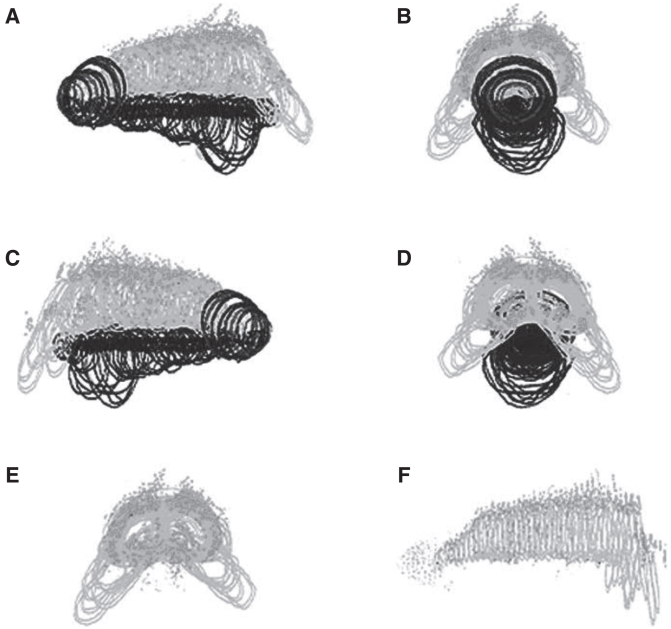
These result from abnormalities in gonadal development. In these disorders, the karyotype is normal (ie, 46,XX or 46,XY). However, mutations in the sex chromosomes or autosomes, teratogens, or trauma to the gonads interfere with their normal development. These disorders are summarized in Table 43–2.

C. Disorders of Phenotypic Sex

These result from abnormalities in hormonal production or activity. The etiologies include defective synthesis by the gonads, abnormal production by the adrenal glands, the presence of exogenous sources, or abnormalities in receptor activity. These disorders are summarized in Table 43–3.

CLINICAL EVALUATION OF PATIENTS WITH ATYPICAL ATYPICAL GENITALIA

The accurate diagnosis of a patient with atypical genitalia is a challenging process. According to the diagnosis, decisions will be made for gender assignment, which will



▲ **Figure 43–7.** Normal human fetal penis, 45 weeks' gestation. Four views of a computer-generated three-dimensional reconstruction (***A***, side; ***B***, front; ***C***, side; ***D***, back, ***E***, front [without urethra]; ***F***, side [without urethra]). Note the nerves (*red*) along the outside of the tunica of the corporeal bodies (*blue*) and their absence at the 12 o'clock position. Note the impressive glandular innervation in ***E*** and ***F*** (urethral lumen in *yellow*, spongiosum and glans in *green*).

have a great impact not only on the patient but also on the patient's family (Daaboul and Frader, 2001; Morland, 2001; Conte and Grumbach, 2007). In most societies, the accepted norm is two sexes, either male or female. When a new baby arrives and the proclamation as to whether it is a boy or a girl cannot be made immediately, an anticipated celebration turns into a stressful family dilemma. With prenatal amniocentesis and routine ultrasound, sex determination is often known well before birth. This can compound the emotional trauma when the known and anticipated genotype does not match the newborn's phenotype. Furthermore, in cases such as severe salt-wasting congenital adrenal hyperplasia (CAH), accurate diagnosis is lifesaving.

History

A detailed history is of great importance. Since many of the disorders such as XX male sec reversal syndrome and ovotesticular syndrome are hereditary, a family history should be carefully examined for similarly affected individuals, unexplained death during infancy, infertility, amenorrhea, and hirsutism. Furthermore, drugs ingested during pregnancy (such as progesterone) and virilizing signs in the mother during pregnancy should be ascertained.

Physical Examination

The abdomen and rectum should be carefully palpated for midline structures such as a uterus. These examinations will provide information regarding the presence of Müllerian duct derivatives. Other helpful physical findings include dehydration, failure to thrive, pigmentation (in patients with salt-wasting CAH), and the presence of other associated anomalies such as cardiac murmurs or web neck (in patients with Turner's or Klinefelter syndrome).

It is important to palpate for gonads in the labioscrotal fold or the scrotum. Since ovaries do not descend, it is likely to be a testis and hence unlikely to represent a case of 46,XX DSD (previously described as female pseudohermaphroditism). Based on the presence or absence of gonads, an algorithm can be followed to determine the differential diagnosis of patients with atypical genitalia (Figure 43–8). It is important to look at the size of phallus (Table 43–4) and the location of the urethral meatus (Camurdan et al, 2007). Any patients with bilateral cryptorchidism or with unilateral cryptorchidism with hypospadias should be suspected of having abnormalities in sexual differentiation. As noted, other helpful physical findings include hyperpigmentation of the areola and labioscrotal fold, common in patients with CAH.

Table 43–1. Disorders of chromosomal sex.

Disorder	Pathology	Chromosomes	Incidence	Gonads	Internal genitalia	External genitalia	Other features	Risk of cancer	Treatment
47,XXY (Klinefelter syndrome)	Extra X chromosome	47,XXY 46,XY/47,XXY	1 in 500	Hyalinized testis No spermatogenesis	Wolffian	Male	Gynecomastia Tall stature Mild mental retardation Elevated FSH/LH Low testosterone Elevated estradiol Infertility	Breast Extragonadal germ cell	Supplemental androgens Surgery for severe gynecomastia
XX male (XX sex reversal)	No Y chromosome Usually TDF (+)	46,XX	1 in 20,000–24,000	Hyalinized testis No spermatogenesis	Wolffian	Male	Gynecomastia Short stature Increased incidence of hypospadias Normal mental status May be familial	Rare germ cell	Same as Klinefelter
45,X (Turner's syndrome)	Absence of X chromosome	45,X 46,XX/45,X Some contain Y-chromosome elements	1 in 2700	Streak gonads No germ cells	Müllerian	Immature female	Short stature Minimal breast development Web neck and other somatic abnormalities Cardiovascular abnormality (ie, coarctation) Renal abnormality (horseshoe or malrotation) Autoimmune disorders (hypothyroid, diabetes) Infertility Amenorrhea	Germ cell Y-chromosome mosaic	Supplemental estrogen Removal of streak gonads in Y-chromosome mosaic
45,X/46,XY DSD (Mixed gonadal dysgenesis)	Incomplete virilization and Müllerian regression	45,X/46,XY (70%) Undetected mosaic	—	One testis (usually undescended) and streak gonad	Wolffian and Müllerian	Usually atypical	Somatic features like 45,X	Germ cell	Female —Prophylactic gonadectomy Male —Streak gonads removed —Intra-abdominal testis excised unless it can be relocated and no ipsilateral Müllerian structure is present
Ovotesticular DSD (true hermaphrodite)	Unknown	46,XX (70%) 46,XY (10%) Mosaic	Unknown	Bilateral ovotestis Ovotestis and ovary or testis (40%) One ovary and testis (40%)	Wolffian and Müllerian	Usually atypical	Gynecomastia at puberty Menstruation at puberty May be familial	Rare germ cell	Reconstructive surgery Possibly remove gonads

Table 43–2. Disorders of gonadal sex.

Disorder	Pathology	Chromosomes	Incidence	Gonads	Internal genitalia	External genitalia	Other features	Risk of cancer	Treatment
Complete gonadal dysgenesis (Swyer syndrome)	Unknown mutation prevents normal differentiation of gonads	46,XX 46,XY	1 in 8000	Bilateral streak gonads	Müllerian	Immature female	Normal to tall stature Minimal somatic abnormal Female: estrogen deficiency Male: testosterone deficiency May be familial	Germ cell in 46,XY	Estrogen supplement Remove gonads in 46,XY
Absent or vanishing testes syndrome	Mutation, teratogen, or trauma to testis	46,XY	Unknown	Absent/rudimentary testis No streak gonads	Wolffian	Varied virilization	Normal	Usually none	Female —Estrogen supplement —Reconstructive surgery Male —Androgen supplement

Chromosomal Evaluation

Examination of buccal mucosal cells for Barr body (inactivated second X chromosome) cannot be relied on to make an accurate diagnosis in patients with atypical genitalia.

A more accurate but more time-consuming method (2–3 days) is the direct assessment of chromosomes from cultured peripheral blood leukocytes. This method provides the exact chromosomal complements, the presence of mosaicism, and structural features of the chromosomes.

In the case of mosaicism, several different tissue samples may be required to accurately confirm the genotype.

Biochemical Evaluation

In the case of CAH, the specific enzyme defect can be determined by the presence or absence and the type of steroid excreted in the urine. Figure 43–9 depicts the steroid synthesis pathway from cholesterol to aldosterone, steroids, or DHT. Note the enzymes necessary for conversion from precursors to products (see also Table 43–3).

In other disorders caused by hormonal abnormalities (such as 5α-reductase deficiency and androgen resistance), direct measurement of plasma testosterone is seldom helpful, since abnormalities in testosterone levels in these pathologic states have not been consistently characterized. A more useful test is the testosterone response following stimulation by human chorionic gonadotropin (hCG) (2000 IU/day for 4 days). If plasma testosterone levels rise >2 ng/mL from baseline, the abnormality is consistent with androgen resistance rather than a defect in testosterone synthesis. In addition, this test is also used to diagnose 5α-reductase type 2 deficiency. A post-hCG stimulation ratio of testosterone to DHT >30 is consistent this diagnosis which can now be confirmed by genomic seque3ncing of the 5 alpha reductase gene..

Radiographic Evaluation

In patients with DSD, ultrasonography provides the least invasive and safest means of imaging the abdomen and pelvis. Identification of Müllerian structures such as the uterus and fallopian tubes will be important in determining the diagnosis (Figure 43–10A). The adrenal glands can also be examined for enlargement. While this finding is not diagnostic for CAH, it is suggestive and can direct further evaluation. Magnetic resonance imaging can provide a more detailed examination of the abdomen for internal genital structures. However, in most cases, anesthesia is needed for a good-quality magnetic resonance imaging examination. Injecting radiographic contrast material through the opening in the urogenital sinus is helpful in delineating the internal duct structures. It is most useful in assessing the presence of vagina, cervix, fallopian tube, utricle, and the connection with the urethra (Figure 43–10B,C). Genitography will also provide needed anatomical information for future reconstructive surgery.

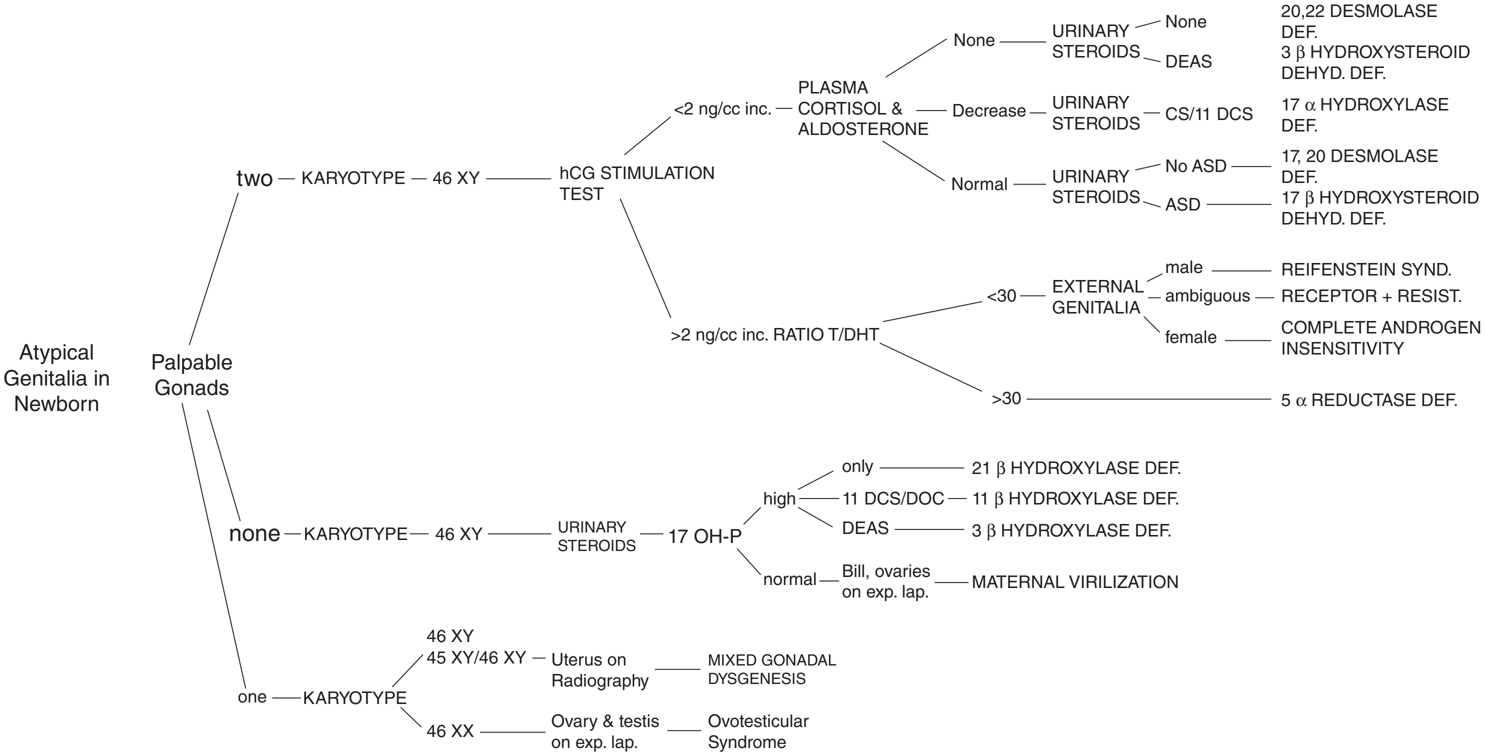
Diagnostic Laparotomy or Laparoscopy

Occasionally, surgery is needed to delineate the internal genitalia and obtain a biopsy specimen of the gonads. It is indicated in patients in whom the biopsy result will influence sex assignment. In addition, surgery may be needed to remove streak or dysgenetic gonads in patients who are

Table 43–3. Disorders of phenotypic sex.

Disorder	Pathology	Chromosomes	Incidence	Gonads	Internal genitalia	External genitalia	Other features	Urinary steroids	Risk of cancer	Treatment
46,XX DSD (Female Pseudohermaphrodite)										
3β-Hydroxysteroid dehydrogenase deficiency	Excess androgens	46,XX	Second most common of CAH	Ovary	Müllerian	Atypical	Severe salt wasting No cortisol No aldosterone	DEAS	None	Replacement mineralocorticoids and glucocorticoids Reconstruction as needed
11β-Hydroxylase deficiency	Excess androgens	46,XX	Rare	Ovary	Müllerian	Atypical	Hypertension Decreased cortisol Decreased aldosterone	11 DCS 11 DOC	None	Replacement glucocorticoids
21α-Hydroxylase deficiency, partial	Excess androgens	46,XX	1 in 5000–15,000	Ovary	Müllerian	Atypical	Normal cortisol Increased aldosterone	17 OH-P	None	Reconstruction as needed
____severe	Excess androgens	46,XX		Ovary	Müllerian	Atypical	Severe salt wasting Decreased cortisol Decreased aldosterone	17 OH-P	None	Replacement mineralocorticoids and glucocorticoids Reconstruction as needed
Excess maternal androgens	Excess androgens	46,XX		Ovary	Müllerian	Atypical	Drugs such as progestational agents Virilizing ovarian Adrenal tumors	None	None	None
46,XY DSD (Male Pseudohermaphrodite)										
20,22-Desmolase deficiency	Defect in testosterone synthesis	46,XY		Testis	Wolffian	Atypical	Severe salt wasting No cortisol No aldosterone	None	None	Replacement mineralocorticoids and glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency	Defect in testosterone synthesis	46,XY	Second most common in CAH	Testis	Wolffian	Atypical	Severe salt wasting No cortisol No aldosterone	DEAS	None	Replacement mineralocorticoids and glucocorticoids Reconstruction as needed
17α-Hydroxylase deficiency	Defect in testosterone synthesis	46,XY		Testis	Wolffian	Atypical	Hypokalemic alkalosis Hypertension Decreased cortisol Decreased aldosterone Gynecomastia	CS 11 DCS	None	Replacement glucocorticoids

17,20-Desmolase deficiency	Defect in testosterone synthesis	46,XY	Rare	Testis	Wolffian	Atypical	Normal cortisol and aldosterone		None	Supplemental testosterone
17β-Hydroxysteroid dehydrogenase deficiency	Defect in testosterone synthesis	46,XY	Most common	Testis	Wolffian	Atypical	Virilization and puberty	ASD	None	Decision reared as female or male
5α-Reductase deficiency	Defect in androgen action	46,XY —Autosomal rec.		Testis with spermatogenesis	Wolffian	Female	Gynecomastia Normal testosterone Virilization at puberty	None	None	None
Complete androgen Insensitivity syndrome	Androgen receptor defect	46,XY —X-linked	1 in 20,000–64,000	Testis not fertile	Absent	Female reared as female	Increased testosterone Increased estrogen	None	Germ cells	Remove gonads after puberty Estrogen replacement
Partial androgen insensitivity syndrome	Androgen receptor defect	46,XY —X-linked receptor	1/10th of complete	Testis not fertile	Wolffian	Female Versus severe hypospadias	Increased testosterone Increased estrogen	None	Germ cells	Depends on sex of rearing
Infertile male syndrome	Androgen receptor defect	46,XY —? X-linked receptor		Testis not fertile	Wolffian	Male	Infertility Normal or increased testosterone Normal or increased estrogen	None	None	None
Persistent Müllerian duct syndrome	Persistent Müllerian ducts	Unknown		Testis	Wolffian with rudimentary uterus and tubes	Male usually cryptorchid	Normal testosterone Normal estrogen	None	None	Orchiopexy Leave uterus and tubes



▲ **Figure 43–8.** Clinical approach to DSD. Algorithm based on palpating gonads. Bil. = bilateral; CS/11 DCS = corticosterone/deoxycortisol; DEAS = 1,3-bis[4-(diethylamino)-2-hydroxy phenyl]-2,4-dihydroxycyclobutenediylium dihydroxide, bis(inner salt); DCS/DOC = deoxycortisol costerone; def. = deficiency; dehyd. = dehydration; 17 OH-P = 17 hydroxyprogesterone; exp. lap. = exploratory laparoscopy; resist. = resistance; synd. = syndrome; T/DHT = testosterone/dihydrotestosterone.

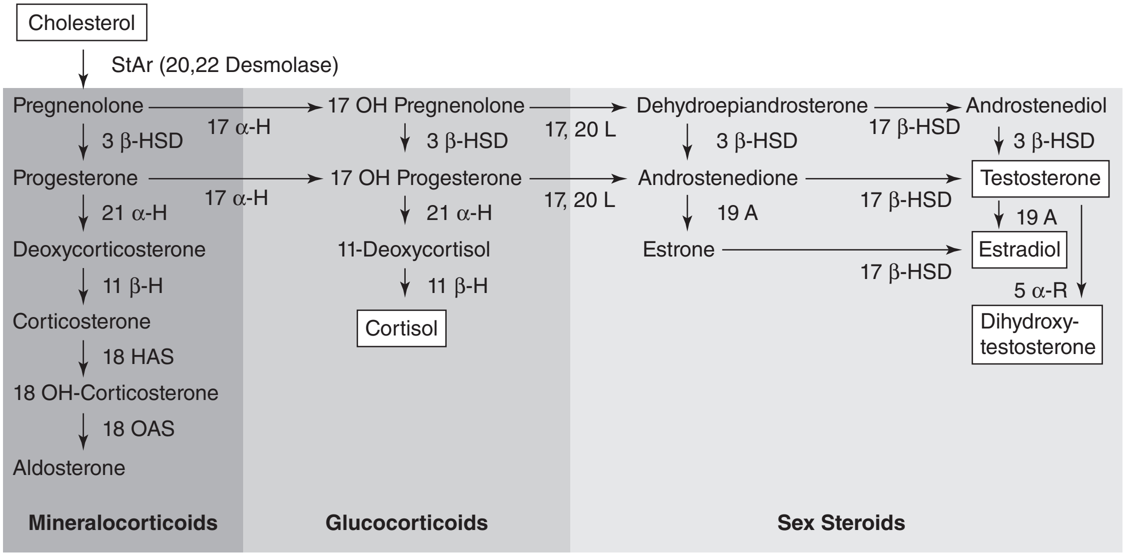
Table 43–4. Normal values for stretched penile length.

Age	Length (cm) (mean ± SD)
Premature 30 weeks	2.5 ± 0.4
Full-term newborn	3.5 ± 0.4
0–5 months	3.9 ± 0.8
6–12 months	4.3 ± 0.8
1–2 years	4.7 ± 0.8
2–3 years	5.1 ± 0.9
3–4 years	5.5 ± 0.9
5–6 years	6.0 ± 0.9
10–11 years	6.4 ± 1.1
Adult	12.4 ± 2.7

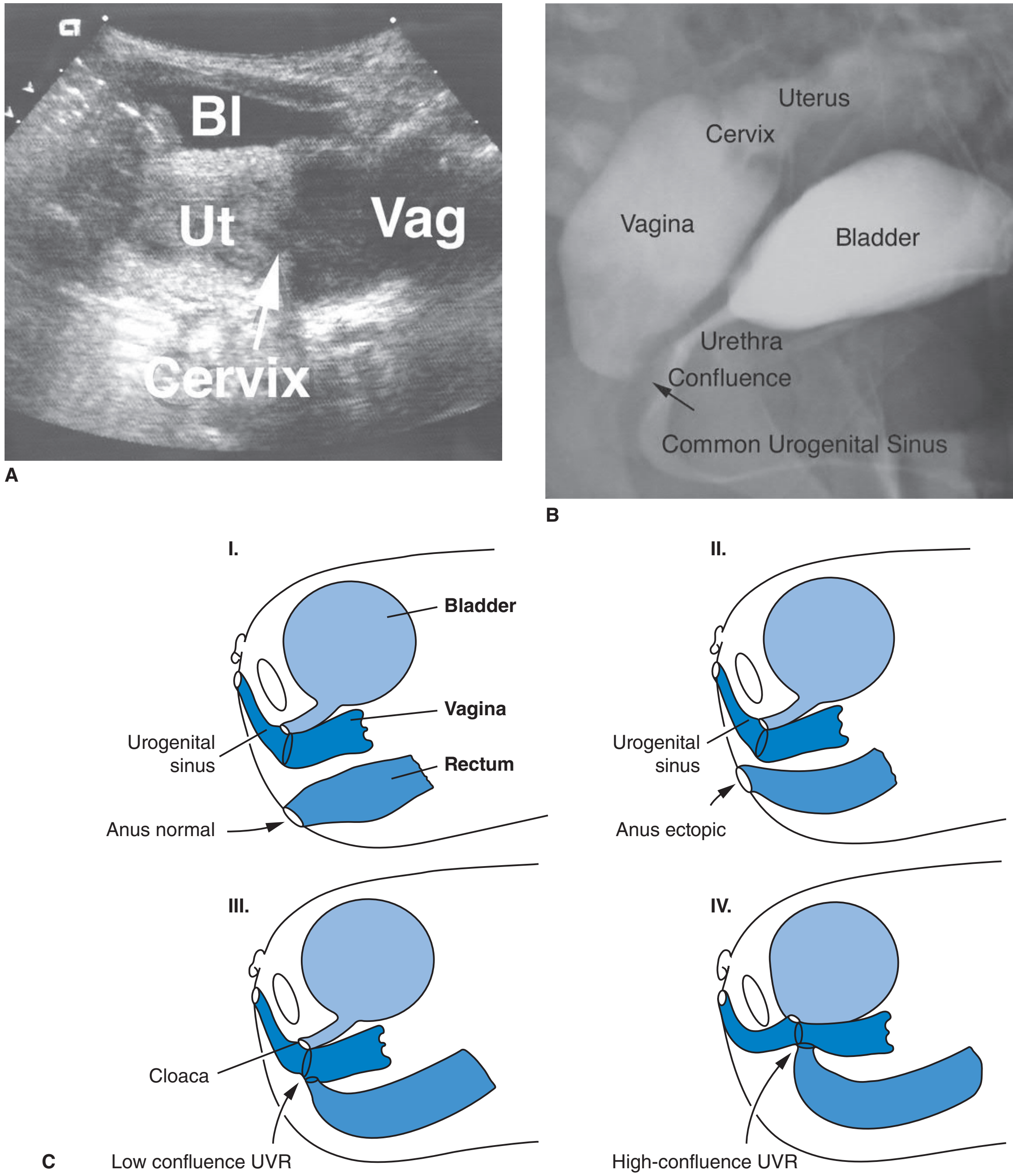
at risk for cancer (Turner's Y variant (Swyer's Syndrome)). Laparoscopic surgery has provided an alternative to open surgery in patients with DSD. It can be performed safely in newborns and requires only one to three 2–3-mm incisions for placement of the laparoscopic ports. Simple surgical procedures such as hernia repair, orchidopexy, and resection of discordant organs can be readily performed laparoscopically.

Sex of Rearing

In the past, the baby born with atypical genitalia was considered incomplete until either a male or female sex was assigned. Unfortunately, a prompt but inappropriate assignment, although timely and comforting for family, physicians, nurses, and staff, can lead to more complex problems in the future. The issue of sexual determination remains complex. We continue to advocate for an immediate and thorough attempt to make a definitive and accurate diagnosis. Fortunately, for most patients with atypical genitalia (ie, CAH), this can be accomplished (Auchus et al, 2010). In patients where ambiguity remains after initial testing and the diagnosis cannot be made, or when the diagnosis is clear but sex of rearing remains unknown, we would advocate for a more cautious approach. Foremost, this would include a reversible or nonbinding sex of rearing. Experience has shown that patients themselves may reassign their sex. For example, in cases of cloacal exstrophy or iatrogenic penile injuries, past treatment was based on the absence of an "adequate" phallic structure. These patients were converted from genetic males to females with surgical orchiectomy, removal of any excess male genitalia, vaginoplasty, and future hormonal treatment for breast development. Although surgical results can be anatomically successful, these patients who were "assigned" a female gender will not menstruate or have fertility potential, and their sexual function is not known. A number of these patients went through adolescence, have identified as females, and had no major issues with



▲ **Figure 43–9.** Pathway of steroid hormone biosynthesis and possible enzyme deficiencies. 3β-HSD = 3β-hydroxysteroid dehydrogenase; 21α-H = 21α-hydroxylase; 11β-H = 11β-hydroxylase; 17β-HSD = 17β-hydroxysteroid dehydrogenase; 18 HAS = 18 hydroxyaldosterone synthetase; 18 OAS = 18 oxidase-aldosterone synthetase; 5α-R = 5α reductase; 19A = 19 aromatase; StAR = steroidogenic acute regulatory protein.



▲ **Figure 43–10.** ***A:*** Newborn sonogram revealing a uterus (Ut) behind the bladder (Bl) in a patient with congenital adrenal hyperplasia. Note the dilated vagina (Vag), the cervix (*arrow*), and the bladder. ***B:*** Genitogram showing a high confluence (*arrow*) of the urethra and vagina with a long common urogenital sinus in a patient with congenital adrenal hyperplasia. ***C:*** Schematic representation of possible genitogram findings. I,II: Urogenital sinus anomalies with two openings on the perineum (common urogenital sinus and rectum). III,IV: Cloacal anomalies with one perineal opening. Note the low and high confluence of the urethra, vagina, and rectum (UVR). Genitogram showing the common urogenital sinus. (Used with permission from Dr Hardy Hendron.)

their assigned discordant, genetic sexual identity. In contrast, some of these patients have subsequently identified with their genetic sex and demanded or reassigned their sex from female to male. In cases where the genotype does not match the phenotype, surgical reconstruction from male to female clearly does not guarantee a successful sexual identity.

The clinical experience exemplifies the complexity of sexual determination. It is evident that social factors, or the "nurturing" hypothesis, and biologic factors, or the "genetic" hypothesis, play a role in determining our sexual identity. The nurturing hypothesis is based on the parent's perception of their child's genitalia. This perception will influence interactions such as naming, clothes, play orientation, and social organization. Clearly, how a parent perceives his or her child and the type of environment used to raise the baby is critical to the child's identity.

In contrast, the genetic hypothesis states that sexual identity is predetermined by the genetic makeup. Increasing laboratory evidence is accumulating to support the genetic hypothesis. For example, animal experimentation supports the concept of steroid or androgen imprinting of the brain. Thus, the process of sexual identity in both humans and experimental animals is not an all-or-none process, meaning that male and female characteristics exist as a continuum.

Practical Approach to the Diagnosis of Disorders of Development

In the newborn period, patients with atypical genitalia can be approached in a logical fashion (Figure 43–11) (Lee et al, 2006). As noted earlier, history, physical examination, laboratory evaluation, and radiographic and in some cases surgical exploration are necessary to make an accurate diagnosis. Once the karyotype is known, along with the gonadal status, appropriate testing can lead to a diagnosis (see Figure 43–11 and Table 43–5). Patients may also present at puberty (inappropriate or delayed development) with sexual differentiation abnormalities or later in life with infertility. The differential diagnosis for these disorders is illustrated in Figure 43–12.

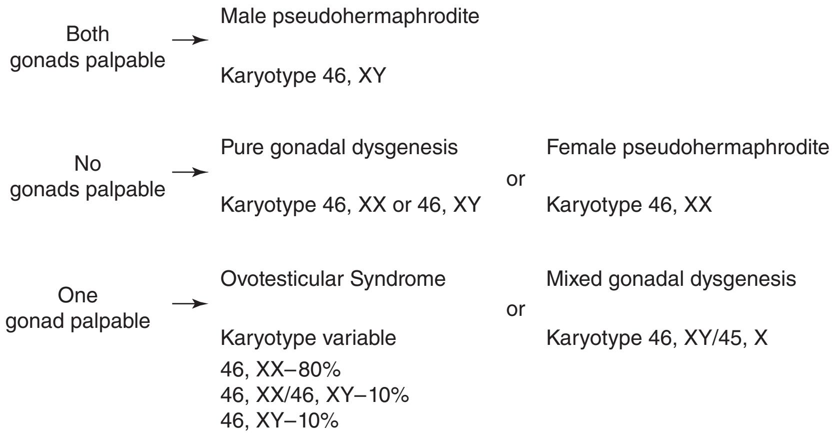
TREATMENT OF SPECIFIC DISORDERS

46,XX DSD (Formerly, Female Pseudohermaphrodites)

The 46,XX disorders of sex development (DSD) are characterized by a 46,XX genotype, nonpalpable gonads or normal ovaries, and variable degrees of virilization of the external genitalia.

A. Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is the most common cause of female atypical genitalia and accounts for approximately 70% of all cases of atypical genitalia. Mutations in one of five genes result in impaired cortisol secretion, which, in turn, causes excess secretion of adrenocorticotropic hormone (ACTH) and consequently adrenal hyperplasia (Speiser, 2007). Four of the five genes code for enzymes necessary for steroid hormone synthesis, and the fifth encodes for an intracellular cholesterol transport protein (StAR) (Figure 43–9). Deficiencies in 21α-hydroxylase and 11β-hydroxylase result in masculinization of the female fetus, while they have no effects on the genitalia of the male fetuses. In contrast, infants with deficiencies in 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and StAR have defects in both the synthesis of cortisol and steroid hormones. Affected males have varying degree of atypical genitalia due to deficiency in testosterone synthesis, while affected females may or may not be virilized.



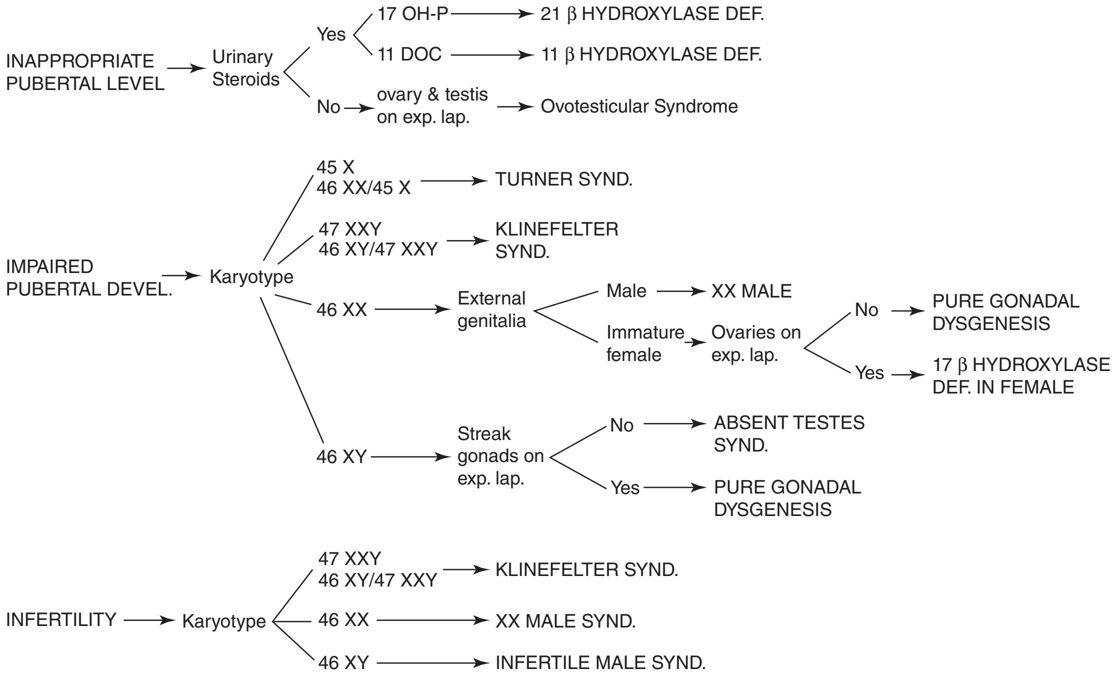
▲ **Figure 43–11.** Algorithm for initial workup of disorders of sex development (DSDs) based on physical examination and karyotype.

Table 43–5. Differential diagnosis for a newborn with ambiguous genitalia.

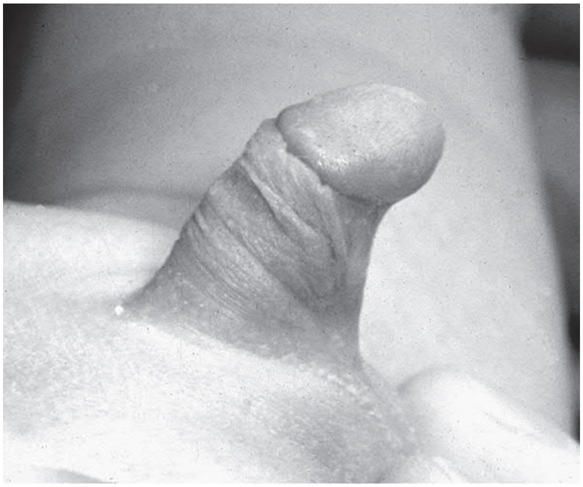
Disorder	Common karyotype	Gonad status	Genitalia	Uterus	Urinary/serum steroids
46,XX DSD (female pseudohermaphrodite) (CAH)	XX	Ovary	Hypospadias	Present	Elevated
46,XY DSD (male pseudohermaphrodite)	XY	Testes	Hypospadias/ micropenis	Absent	Normal
45,X/46,XY DSD (mixed gonadal dysgenesis	XY/XO	Streak dysgenetic	Hypospadias	Variable/rudimentary	Normal
Ovotesticular DSD (true hermaphrodite)	XX/mosaic	Ovotestis or ovary and testes	Hypospadias	Variable/rudimentary	Normal

21α-Hydroxylase deficiency is the most common cause of CAH, accounting for 90% of all cases. The metabolites 17-hydroxyprogesterone and 17-hydroxypregnelone, which build up above the 21α-hydroxylase deficiency, are metabolized to androgens, resulting in virilization of the female external genitalia. Three forms of 21α-hydroxylase deficiency exist: classic, simple virilizing, and nonclassic. Each of these disorders is characterized by the activity level of the gene. Patients with the classic disease have both virilization and salt wasting, those with simple virilizing have masculinization without salt loss, and the nonclassic patients present after puberty with virilization.

In general, the classic form of 21α-hydroxylase deficiency exhibits the more severe forms of virilization (Figure 43–13). Impaired cortisol and aldosterone secretion leads to electrolytes and fluid losses, producing hyponatremia, hyperkalemia, acidosis, increased plasma renin, dehydration, and eventual vascular collapse unless recognized and treated. In affected males, deficiency in 21α-hydroxylase does not result in abnormal genitalia, and consequently, salt loss may occur unnoticed. Aggressive fluid resuscitation with normal saline should be instituted immediately, and repeat serum electrolyte measurement should be obtained to monitor the progress of the resuscitation. Diagnosis is based on an elevated level of 17-hydroxyprogesterone in the



▲ **Figure 43–12.** Differential diagnosis of patients with inappropriate pubertal development, impaired pubertal development, and infertility. Def. = deficiency; devel. = development; DOC = 11-deoxycorticosterone; exp. lap. = exploratory laparoscopy; 17 OH-P = 17 hydroxyprogesterone; synd. = syndrome.



▲ **Figure 43–13.** Patient with severe masculinization from congenital adrenal hyperplasia.

urine and blood. After diagnosis and stabilization, replacement therapy should be instituted with glucocorticoids, mineralocorticoids, and salt. Regular measurement of serum electrolytes, renin, and ACTH helps monitor the adequacy of hormonal replacement. Untreated patients with 21α-hydroxylase deficiency exhibit excessive growth, virilization, advanced bone age, and early closure of epiphyseal growth plates (Hughes, 2007).

11β-Hydroxylase deficiency accounts for most of the remaining cases of CAH (approximately 9%). Patients with 11β-hydroxylase accumulate 17-hydroxyprogesterone as well as DOC and 11-deoxycortisol, which results in salt accumulation leading to hypertension. Patients with 11β-hydroxylase deficiency are more likely to present with hypertension secondary to the salt-retaining metabolites DOC and 11-deoxycortisol, in contrast to the hypovolemic shock associated with 21α-hydroxylase deficiency. Hypokalemia is also common secondary to an increase in mineralocorticoid activity.

Since CAH is hereditary, it is possible to counsel and offer treatment to families wishing to have additional children. Maternal treatment with dexamethasone prior to the 10th week of gestation can significantly reduce the risk of masculinization of the female fetus (Miller, 1998). Standard prenatal treatment is 20 mg/kg twice daily beginning as soon as the pregnancy is confirmed (gestation week 5) in a family with a positive history of CAH. At 9–10 weeks' gestation, chorionic villus sampling can confirm karyotype and test for the presence of the gene *CYP21*, which is present in 21α-hydroxylase deficiency (90% of CAH cases). If the karyotype is XY or the CAH gene *CYP21* is not present, the maternal dexamethasone treatment is stopped. Statistically, 50% of the fetuses will be male, and of the females, only 25% will be affected secondary to the recessive inheritance pattern of 21α-hydroxylase deficiency. Unfortunately, this will result in unnecessary prenatal steroid exposure in seven of eight fetuses with unknown long-term health consequences, such as hypertension. Although the short-term success of decreasing female virilization has been documented, long-term follow-up of fetuses exposed to steroids needs to be documented.

B. Maternal Hormonal Sources of Virilization

Maternal tumors are a rare cause of virilization of the female fetus. The most common type are luteomas of the ovary, which also virilize the mother. Diagnosis can be made by maternal blood samples and imaging studies (sonogram and magnetic resonance imaging). Maternal ingestion of medication is another rare cause of abnormalities in genital development (Table 43–6). Progesterone is a common agent currently used early in pregnancy to prevent abortions as well as during in vitro fertilization treatments.

The female fetus that is exposed to high concentrations of progesterone can virilize secondary to direct action of progesterone on the AR. In the male fetus, hypospadias can develop by progesterone-inhibiting testosterone synthesis and downregulating the AR. A prenatal history of progesterone exposure should be elicited in the differential diagnosis of patients with abnormalities of the external genitalia.

▶ 46,XY DSD (Formerly, Male Pseudohermaphrodites)

The 46,XY DSDs are characterized by a 46,XY genotype, normal testes (usual palpable), and partial or complete masculinization of the external genitalia. The differential diagnosis is outlined in Figure 43–14.

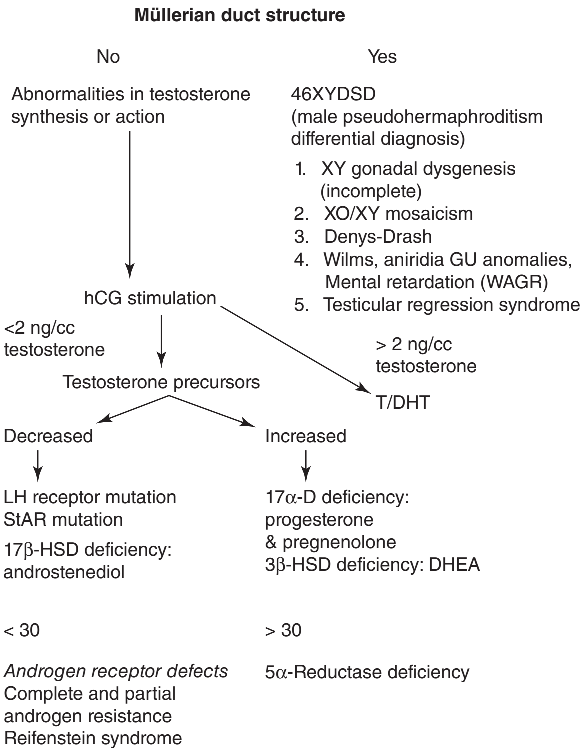
Two forms of androgen resistance related to male pseudohermaphrodites are complete androgen insensitivity and partial androgen insensitivity.

A. Complete Androgen Insensitivity

Androgen resistance ranges from partial to complete owing to a defect in the AR. Patients with complete androgen resistance or androgen insensitivity syndrome (AIS) (previously called **testicular feminization**) have a 46,XY karyotype but have unambiguous female external genitalia, hypoplastic labia majora, a blind vaginal pouch, and an absent uterus

Table 43–6. Drugs that may induce disorder of sex development if taken during pregnancy.

C21-steroid medroxyprogesterone acetate (progesterone)
Finasteride (Proscar)
Leuprolide acetate (Lupron)
Stilbestrol
Danazol
Norethynodrel
Ethisterone
Norethindrone


Müllerian duct structure
No
Yes
Abnormalities in testosterone synthesis or action
46XYDSD (male pseudohermaphroditism differential diagnosis)
1. XY gonadal dysgenesis (incomplete)
2. XO/XY mosaicism
3. Denys-Drash
4. Wilms, aniridia GU anomalies, Mental retardation (WAGR)
5. Testicular regression syndrome
hCG stimulation
<2 ng/cc testosterone
> 2 ng/cc testosterone
Testosterone precursors
T/DHT
Decreased
Increased
LH receptor mutation
StAR mutation
17β-HSD deficiency: androstenediol
17α-D deficiency: progesterone & pregnenolone
3β-HSD deficiency: DHEA
< 30
> 30
Androgen receptor defects
Complete and partial androgen resistance
Reifenstein syndrome
5α-Reductase deficiency

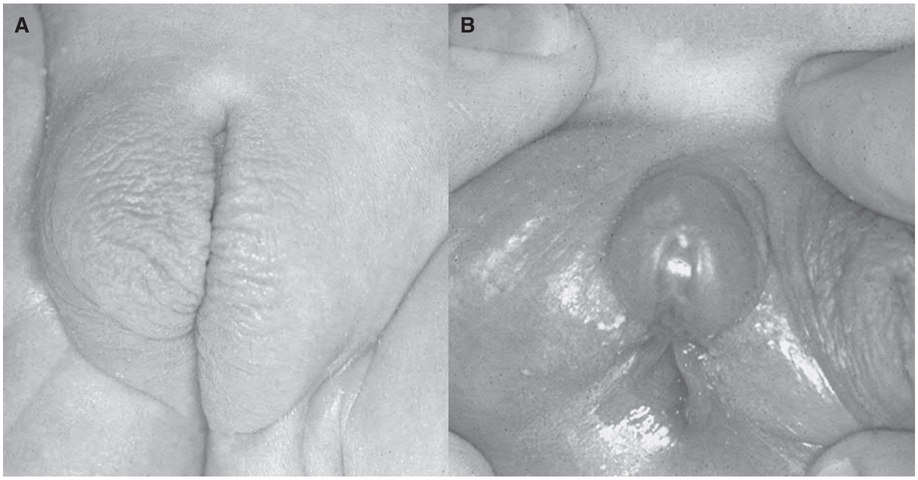
▲ **Figure 43–14.** Differential diagnosis of patients with 46 XY DSD (male pseudohermaphroditism). 17α-D = 17(α)-hydroxylase; DHEA = dehydroepiandrosterone; GU = genitourinary; hCG = human chorionic gonadotropin; HSD = hydroxy-steroid dehydrogenase; LH = luteinizing hormone; StAR = steroidogenic acute regulatory protein; T/DHT = testosterone/dihydrotestosterone.

(Wisniewski et al, 2000). Since a functional AR is necessary for the development of axillary and pubic hair, complete AIS patients have sparse to nonexistent hair growth in these areas. Complete AIS patients either inherit the disease by an X-linked recessive pattern or develop a spontaneous mutation that renders the AR nonfunctional. Patients with complete AIS appear to identify as females. Presumably, the functional defect in the AR also exists in the brain, preventing "masculinization." There is not enough long-term follow-up to assess issues with sexual identity in these patients.

Complete androgen resistance should be suspected in phenotypic females who present with an inguinal hernia that contains a testis (approximately 1% of all prepubertal females undergoing hernia repair) (Oakes et al, 2008). The most common presentation for complete AIS is amenorrhea in adolescent females. Breast development occurs in AIS patients secondary to the peripheral conversion of testosterone to estradiol from aromatase enzyme. After puberty, the testes have approximately a 10% risk of developing cancer; the most common tumor is a seminomatous germ cell (Kathrins and Kolon, 2016). Because of the significantly increased cancer risk, removal of the gonads is recommended after postpubertal breast development. Alternatively, the gonads can be removed at the time of diagnosis, with estrogen replacement therapy initiated in the pubertal time period. Since the vagina may be inadequate in length, some patients may need augmentation procedures. Self-vaginal dilation is the most common technique, followed by vaginal augmentation procedures using skin grafts or bowel.

B. Partial Androgen Insensitivity

In contrast to complete AIS, patients with partial androgen resistance may have external genitalia ranging from mild to severe hypospadias (with or without cryptorchidism) to micropenis or clitorimegaly with partial labial fusion (Figure 43–15)



▲ **Figure 43–15.** Partial androgen receptor defect resulting in severe hypospadias with curvature *(**A**)* and a small phallus *(**B**)*.

(Griffin et al, 1995). The testes may be located in the labia, inguinal canal, or abdomen. The testes are histologically normal before puberty. However, after puberty, spermatogenesis is usually absent and there is Leydig cell hyperplasia. The testes are predisposed to malignant transformation in 4–9% of the patients (Fallat and Donahoe, 2006).

The defect in partial androgen resistance is typically due to a single base pair mutation in the AR. Inheritance may be X-linked, autosomal recessive, or from a spontaneous mutation. Interestingly, the same genetic defect within a family may have a different phenotypic expression. The variability of phenotypic expression makes counseling difficult in affected families.

In patients with partial androgen resistance, the sex of rearing depends on the degree of androgen resistance and the degree of genital ambiguity. In patients who respond to high-dose androgen therapy (2 mg/kg initially followed by 4 mg/kg) with phallic growth, the sex of rearing as male has been successful. Genital reconstruction repairing the hypospadias and undescended testes is performed at an early age. Patients who have a poor response to androgen stimulation fall into a difficult category of DSD. In the past, patients who were raised as females had feminizing genital surgery and gonadectomy typically in the first year of life. At the time of puberty, estrogen replacement is instituted. Presumably in partial androgen insensitivity, sexual identity is influenced by the effects of androgens on central imprinting. A discord may exist between the external genitalia that partially responds to androgen stimulation and the effects of androgens on determining sexual identity in the brain (Zucker, 2003). The fact that some patients with severe hypospadias and a small phallus have had difficulty with sexual identity in adulthood renders sex assignment difficult. Presently, it seems reasonable to delay irreversible surgery until after the patient has developed a sexual identity and can drive the decision for reconstructive surgery.

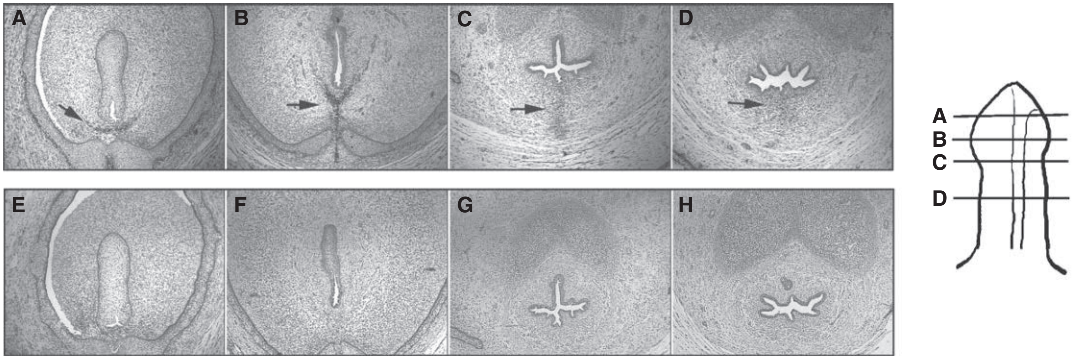
5α-Reductase Type 2 Deficiency

5α-Reductase type 2 deficiency is an autosomal recessive transmitted disorder affecting the formation of the male genitalia (Wilson et al, 1993). 5α-Reductase is responsible for the conversion of the less potent testosterone to the 5–10 times more potent DHT. Type 2 5α-reductase predominates in the tissue of the external genitalia and the prostate, whereas type 1 5α-reductase localizes to the skin and nongenital tissues. Numerous mutations have been described in the 5α-reductase type 2 gene that are consistent with the variation in clinical spectrum seen in patients with this defect. Immunohistochemical localization of 5α-reductase type 2 reveals that the enzyme is contained in the midline urethral seam (Figure 43–16) (Kim et al, 2002). The midline seam localization is consistent with the formation of hypospadias in patients with 5α-reductase type 2 gene defects in that the epithelial edges of the urethral seam would fail to fuse, resulting in hypospadias.

Clinically, patients with 5α-reductase type 2 present with a small phallus, severe hypospadias, bifid scrotum, and a residual prostatic utricle or blind-ending vaginal pouch (Figure 43–17). The testes are often undescended in the inguinal canal. Untreated patients will typically virilize during puberty when elevated levels of the less potent testosterone either overwhelm the functioning androgen gene or the functioning 5α-reductase type 1 enzyme cross-reacts with the excess testosterone, converting it to DHT.

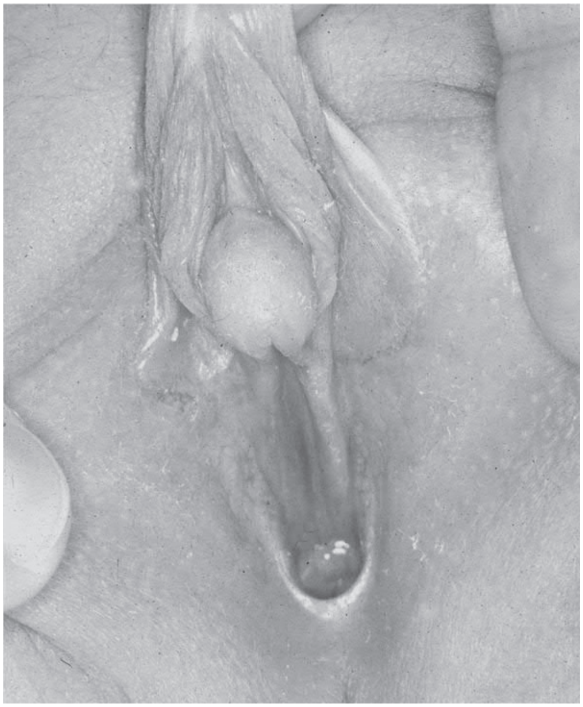
Sexual identity appears to be intact for karyotype XY males with 5α-reductase type 2 deficiency, presumably from an intact masculinization of the brain. In specific geographic areas such as the Dominican Republic, where the incidence of 5α-reductase type 2 deficiency is relatively high, it is generally accepted that these children will change from an initial "in-between" sex to a male sexual identity at the time of puberty.

The diagnosis of 5α-reductase type 2 deficiency should be considered in severe phenotypes of hypospadias, especially



▲ **Figure 43–16.** Immunohistochemical localization of 5α-reductase type 2 ***(A–D)*** and the androgen receptor (AR) ***(E–H)*** in the same human fetal penis at 16.5 weeks of gestation (reduced from 25×). Note the strong expression of 5α-reductase type 2 along the urethral seam area (*arrows*).

in patients with associated scrotal anomalies and undescended testes. Diagnosis is based on an increase in the ratio of testosterone to DHT. Since these patients have a small phallus, attempts at enlargement with DHT cream are reasonable, although DHT is difficult to obtain in the United States. Reconstructive surgery for the hypospadias and undescended testes is indicated. Fertility has rarely been reported in patients with 5α-reductase type 2, secondary to poor sperm production and quality and cryptorchidism.

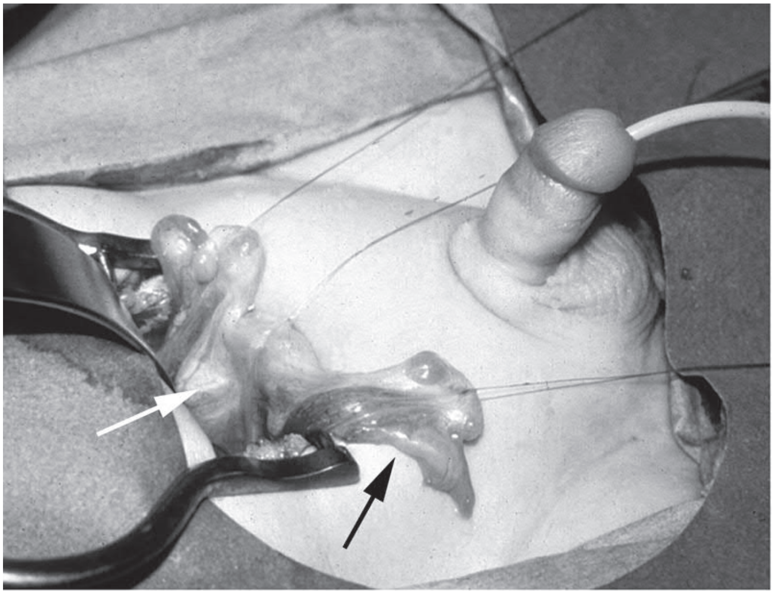


▲ **Figure 43–17.** A patient with 5α-reductase type 2 deficiency. Note severe hypospadias with a small phallus, bifid scrotum, and visible prostatic utricle or blind-ending vaginal pouch.

Persistent Müllerian Duct Syndrome

Müllerian duct-inhibiting substance or factor (anti-Müllerian duct hormone) causes regression of the structures that would have formed the uterus, fallopian tube, and upper part of the vagina. Defects in the MIS gene or MIS receptor result in retained Müllerian structures are typically inherited as an autosomal recessive defect. Male siblings of affected patients, especially those with cryptorchidism, should undergo screening; they have a 25% chance of being affected (Rey et al, 1999).

Clinically, patients with persistent Müllerian duct syndrome present, unexpectedly, at the time of surgery for cryptorchidism (Figure 43–18). Hence, the alternate name for persistent Müllerian duct syndrome is **hernia uterine inguinale**. Within the hernia sac, a fallopian tube, uterus, or both are found attached to the testicular cord structures. What makes the treatment difficult is that these structures and hence the diagnosis are found unexpectedly at the time of surgery for cryptorchidism. If persistent Müllerian duct structures are found during orchiopexy, it is reasonable to



▲ **Figure 43–18.** Hernia uterine inguinale or persistent Müllerian duct syndrome. Note the presence of a fallopian tube (*black arrow*) and uterus attached (*white arrow*) to the testicular cord structures.

abort the procedure until a correct diagnosis can be determined. At the initial exploration, a clear description of gonad and surrounding Müllerian structures should be documented, with a biopsy specimen of the gonad taken and a karyotype obtained.

Once a definitive diagnosis is made, reconstructive surgery can be performed. Separation of inappropriate Müllerian structures from the cord without disturbing the vas deferens, the testicular artery, or both is the goal; however, this may be impossible if the vas runs through the Müllerian structures, which is a common outcome. Fertility is usually impaired in patients with persistent Müllerian duct syndrome even though testosterone levels may be normal. Whether this is a consequence of primary gonadal dysfunction or secondary to the cryptorchid testes is controversial. Efforts should be made to remove the Müllerian structures and deliver the testes into the scrotum or at least a palpable position in the groin for subsequent cancer surveillance. Testes cancer has been reported in 2–10% of patients. In patients where the testes remain in the abdomen or cannot be separated from the Müllerian structures, orchiectomy or long term survelliance should be considered.

▶ Abnormal Gonadal Function Syndromes

A. 45,X DSD (Turner's Syndrome)

Turner's syndrome is relatively common, occurring in 1 in every 2000 female births. The genotype in patients with Turner's syndrome is a complete or mosaic X monosomy, 45,X, or 45,X/46,XX) (Loscalzo, 2008). Turner stigmata consist of a web neck, shield chest, aortic valve defects, coarctation of the aorta, horseshoe kidney, short stature, and absent puberty. During fetal development in patients with Turner's syndrome, the ovaries develop but subsequently degenerate to streak gonads. The streak gonads are not at risk for cancer (unless Y chromatin material is present) and therefore do not need to be removed (Cools et al, 2014). Therapy is directed toward growth augmentation with growth hormone therapy in childhood. Subsequently, estrogen replacement is begun in late adolescence so as not to interfere with maximum growth.

B. 46,XX DSD Complete Gonadal Dysgenesis

Patients with 46,XX complete gonadal dysgenesis are typically diagnosed following a workup for delayed puberty or primary amenorrhea (Wolffenbuttel et al, 2016). Patients have a normal female phenotype without the stigmata of Turner's syndrome, normal external and internal Müllerian structures, and bilateral streak gonads. Sexual identity is female. Unlike patients with 46,XY gonadal dysgenesis, risk of tumor formation is rare and treatment is directed at hormonal replacement, with removal of the streaks gonads unnecessary.

C. 46,XY DSD Gonadal Dysgenesis (Swyer's Syndrome)

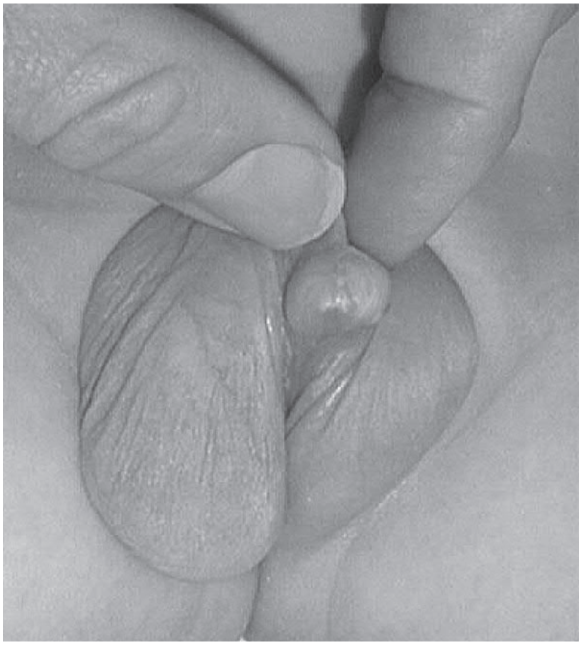
Patients with 46,XY gonadal dysgenesis are characterized by absent testicular function in the presence of a Y chromosome. Classically, patients with 46,XY gonadal dysgenesis have a female phenotype. Patients come to medical attention if the prenatal karyotype (XY) is discordant with the child's phenotype (female), delayed puberty, amenorrhea, or precocious puberty from a hormonally functional gonadal tumor. The incidence of gonadal tumors is as high as 60%; gonadoblastoma is the most common, although dysgerminomas, seminomas, and nonseminomatous germ cell tumors have also been reported.

In pure XY gonadal dysgenesis, Müllerian duct structures usually are present secondary to failure of MIS secretion, and Wolffian duct structures are vestigial or absent secondary to lack of testosterone secretion. Laboratory analysis reveals female levels of baseline testosterone with no increase in response to hCG stimulation. Surgical exploration reveals streak gonads, fallopian tubes, and a uterus. With a 60% chance of tumor, the gonads need to be removed once the diagnosis is confirmed. These patients identify as females and require estrogen replacement at the time of puberty.

D. 45,X/46,XY DSD (Mixed Gonadal Dysgenesis)

Patients with mixed gonadal dysgenesis usually have a 45,X/46,XY, 46,XY, or other mosaic karyotype. They typically have one streak and one dysgenetic testis. Most children with mixed gonadal dysgenesis have incomplete virilization, resulting in atypical genitalia or hypospadias with cryptorchidism. The other classic presentation is a mosaic genotype diagnosed on prenatal amniocentesis (Chang et al, 1990). Interestingly, the subsequent phenotype of patients with a prenatal karyotype of 45,X/46,XY is 90% normal male external genitalia. However, with a prenatal genotype of 45,X/46,XY, the patient is at risk for progressive gonadal changes, leading to fibrosis and decreased fertility and low testosterone levels. The incidence of gonadal tumors does not seem to be increased. Most notably, 20% of these children have mental retardation or autism.

In patients who present with atypical genitalia, one gonad is typically palpable (most commonly on the right side) in the scrotum or inguinal canal, and the other gonad (streak) is nonpalpable. The phallus size is typically small with a proximal or more severe hypospadias (Figure 43–19). Testosterone levels are normal with an appropriate response to hCG. MIS levels are usually normal. At surgery, the dysgenetic gonad (streak) may appear grossly normal but have microscopic abnormalities such as hypoplastic tubules surrounded by ovarian or fibrotic stroma. Variable Müllerian duct structures, such as fallopian tubes and uterus, are present, depending on the degree of gonadal dysgenesis. On biopsy, the contralateral gonad in the scrotum or inguinal canal is either a normal or dysgenetic testis. In patients with mixed



▲ **Figure 43–19.** Presentation of mixed gonadal dysgenesis with atypical genitalia and a unilateral palpable gonad on the right side.

gonadal dysgenesis, the risk of gonadoblastoma is 15–30% (Levin, 2000). Gonadoblastoma is a steroid hormone-secreting gonadal tumor composed of large germ cells, Sertoli cells, and stromal derivatives. The incidence of gonadoblastoma appears to be higher in more undervirilized patients and the most common associated karyotype is 46,XY. In total, 60% of gonadoblastomas arise in an indeterminate gonad, 22% in streak gonads, and 18% in dysgenetic cryptorchid testis. Two cases occurring in a testis located in the scrotum have been reported. One-third of the patients have bilateral disease, and 60% of gonadoblastomas are associated with subsequent malignant germ cell tumor (germinoma, seminoma, and dysgerminoma but also embryonal teratoma, embryonal carcinoma, endodermal sinus tumor, or choriocarcinoma). Metastases develop in 10% of patients with germinomas arising within the gonadoblastoma.

In children who are undervirilized, female sex of rearing is an option, and the streak and dysgenetic gonads should be removed at the time of diagnosis because of increased risk of malignancy. Hormonal replacement with estrogen will be necessary during adolescence. In male sex of rearing, which is the more typical pathway, management of the scrotal testis is controversial, ranging from serial observation to surveillance biopsy. In the virilized patients who are raised as males, the testis will inevitably reveal poor hormonal and fertility potential (Woodhouse, 2001). These patients will require testosterone supplementation in adulthood (Birnbacher et al, 1999).

In 5% of patients, mixed gonadal dysgenesis is associated with Wilms' tumor, atypical genitalia, and progressive glomerulopathy known as the **Denys–Drash syndrome**. Wilms' tumor occurs in the first 2 years of life and is often bilateral. Classic presentation is an infant with atypical genitalia, hypertension, and nephrotic syndrome.

E. 17β-Hydroxysteroid Dehydrogenase Deficiency

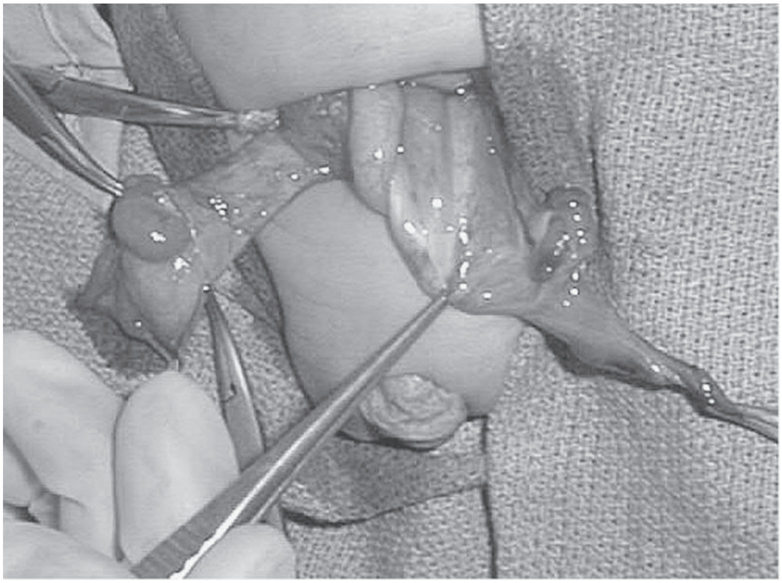
Patients with a defect in the enzyme 17β-hydroxysteroid dehydrogenase do not efficiently convert androstenedione to testosterone. 17β-Hydroxysteroid dehydrogenase is predominantly located in the testes. The rare disorder of 17β-hydroxysteroid dehydrogenase deficiency is inherited via an autosomal recessive pattern. This disorder is indigenous to the Arab population of the Gaza strip in the Middle East. Clinical presentation in a patient with XY genotype is mild virilization of the external genitalia, with clitoral hypertrophy, and a blind-ending utricle (vagina). The testes are undescended in the abdomen or inguinal canal or descended into the labioscrotal folds. If the virilization is mild, the diagnosis becomes apparent at puberty, with penile growth and male secondary sexual characteristics. At puberty, the increased levels of androstenedione are converted by nongenital, nonmutant 17α-hydroxysteroid dehydrogenase to testosterone. These patients may also present with gynecomastia at puberty by the peripheral conversion of androstenedione to estradiol by aromatase. Diagnosis is based on an increased ratio of androstenedione to testosterone postpubertal or in the prepubertal state in response to an hCG stimulation test.

If the diagnosis is suspected in infancy, treatment with testosterone, reconstruction of the hypospadias, and male sex assignment are indicated. At puberty in the Gaza strip, gender conversion from female to male is common practice. Long-term outcomes of patients raised as females initially and reassigned to males at puberty await documentation.

▶ Ovotesticular DSD (True Hermaphroditism)

Ovotesticular DSD is defined as the presence of both ovarian and testicular tissue within the same individual (Figure 43–20). This is the rarest form of DSD and complex in respect to sex of rearing. To confirm a diagnosis of ovotesticular syndrome, the patient will require gonadal biopsy. The most common karyotype in patients with ovotesticular syndrome is 46,XX (predominately in African-Americans), followed by 46,XY/46,XX mosaicism. The latter karyotype in a patient with atypical genitalia strongly suggests the diagnosis of ovotesticular syndrome. Only 7% of patients with this disorder have a 46,XY karyotype. Interestingly, not all patients with ovotesticular syndrome express the SRY gene, suggesting that non-SRY genes play a role in the development of the testes in these patients.

In patients with ovotesticular syndrome, the gonads are a combination of ovotestis, ovaries, and testis. The most common configuration is ovotestis/ovary in 35%, followed by



▲ **Figure 43–20.** Finding at the time of surgical exploration in an ovotesticular syndrome (true hermaphrodite). On the patient's right side, note the testes, and on the left, note the fallopian tube, uterus, and biopsy-proven ovary.

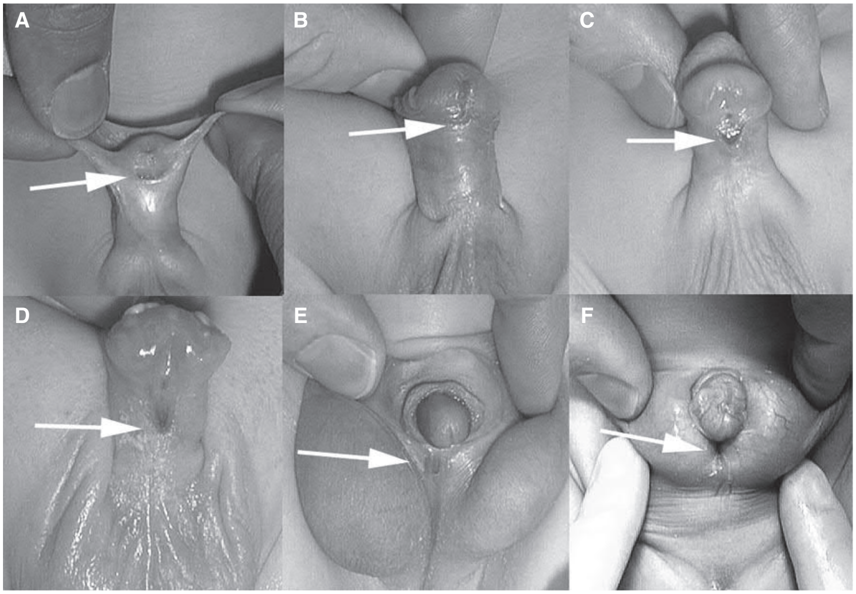
bilateral ovotestis in 25%, ovary/testes in 25%, and ovotestis/testes in the remaining 15%. One or both gonads are palpable in at least 60% of the patients. For unexplained reasons, the testis is more likely to be found on the right side. The testis and ovaries are located in their respective normal positions, and the level of descent of the ovotestis is dependent on the amount of testicular tissue. While ovarian histology and function may be normal, testicular histology and function are usually abnormal. Ovotestis can be bilobar in configuration, with the ovarian and testicular tissue relatively separate, or the ovarian and testicular tissue may be intermingled and difficult to separate surgically. At the time of diagnosis, gonadal biopsy is necessary to determine the histologic status of the gonad. The internal structures tend to correlate with the type of gonad. Approximately 80% of ovotesticular syndrome patients will have a functional or rudimentary uterus. The uterus may be found in the abdomen or associated with an inguinal hernia. In patients with normal uterine structures and ovarian histology, fertility and normal pregnancies have been reported. The external genitalia are usually atypical, although 60% of patients are masculinized, with a well-developed hypospadiac phallus. The hypospadias can be severe perineal or penile scrotal with incomplete fusion of the labioscrotal folds. The degree of masculinization is dependent on the amount of functional testicular tissue present. In childhood, testicular tissue has been documented to have normal spermatogonia. With maturation, however, testicular fibrosis occurs, with fertility in males not reported. Testicular tumor is uncommon, occurring in only 1–2% of the patients.

The diagnosis of ovotesticular syndrome should be suspected in patients with virilized atypical genitalia who have a 46,XX (African-American) or mosaic genotype 46,XX/46,XY associated with the finding of Müllerian structures. Diagnosis is confirmed by gonadal biopsy confirming the presence of both ovarian and testicular tissue. Gonadal tissue inappropriate for sex of rearing should be removed. In patients who are raised as females, removal of all functioning testicular tissue is critical to prevent virilization at puberty. Surgical correction of the urogenital sinus to expose the vagina is necessary. In patients raised as males—who account for approximately 30% of all true hermaphrodites—the hypospadias and undescended testes should be reconstructed. In males, since testicular failure is common at puberty, testosterone supplementation may be required.

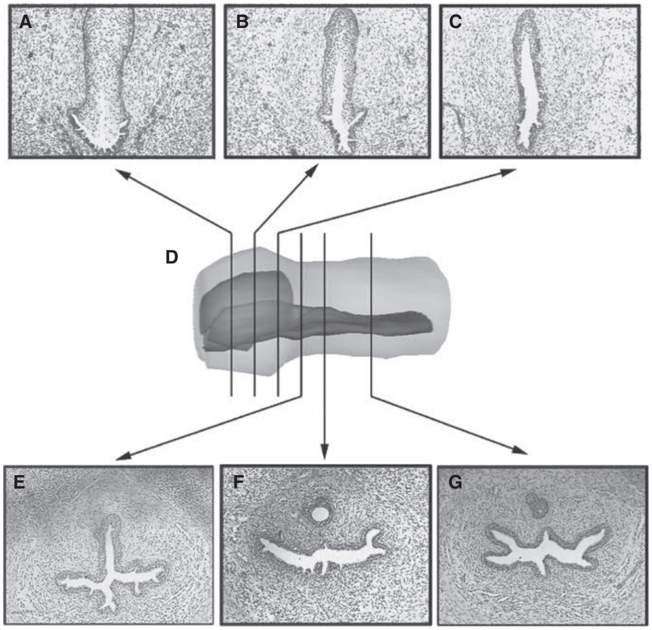
▶ Unclassified Forms of Abnormal Sexual Development

A. Hypospadias

Hypospadias except in the most severe situation is not a form of DSD (Figure 43–21) (Baskin and Ebbers, 2006). The etiology can be defined in less than 5% of patients. This leaves most cases without a defined etiology. The variable expression of the AR in the ventral versus the dorsal urethra may play a role in the etiology of hypospadias (Figure 43–22) (Baskin et al, 1998; Kim et al, 2002). Recent theories suggest an abnormality in closure of the midline urethral seam. Another possible etiology explaining the increase in



▲ **Figure 43–21.** The spectrum of hypospadias, which is not an atypical or a DSD condition. ***A:*** Anterior, where the meatus is on the inferior surface of the glans penis. ***B:*** Coronal, where the meatus is in the balanopenile furrow. ***C:*** Distal, on the distal third of the shaft. ***D:*** Penoscrotal, at the base of the shaft in front of the scrotum. ***E:*** Scrotal, on the scrotum or between the genital swellings. ***F:*** Perineal, where the meatus is behind the scrotum or genital swellings.



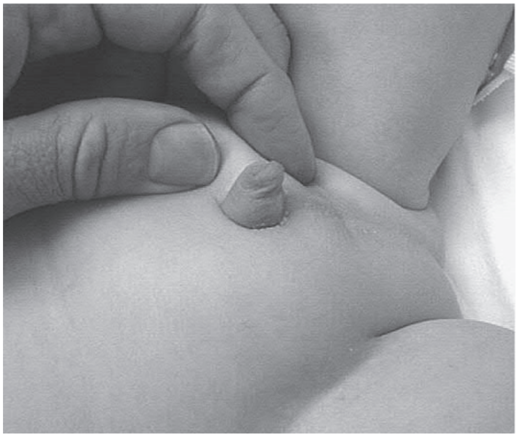
▲ **Figure 43–22.** Androgen receptor (AR) expression in the human fetal penis at 16.5 weeks. A greater density of AR-positive cells is seen in the ventral portion of the urethral epithelium in the distal glans *(**A**)*, midglans *(**B**)*, and proximal glans *(**C**)*. In the distal *(**E**)*, mid *(**F**)*, and proximal *(**G**)* shafts of the penis, all portions of the urethral epithelium show the same density of expression. Three-dimensional reconstruction was performed to demonstrate the urethral AR expression pattern *(**D**)*. Note the weaker density of AR in the dorsal aspect of the glandular urethra.

incidence of hypospadias in Western countries over the last 25 years is an increase in exposure to environmental endocrine disruptors (Baskin et al, 2001).

In controlled studies, most patients with hypospadias undergo successful surgical reconstruction and have acceptable long-term outcomes. Patients with hypospadias have an unambiguous male sexual identity. In severe forms of hypospadias with perineal or scrotal urethral openings, severe curvature and the phallus buried within the scrotum are the critical issues confirming the correct diagnosis. This is also the case for patients with hypospadias and a nonpalpable or undescended testis. If any doubt exists, patients with severe hypospadias, hypospadias in association with an undescended testis, or both, a karyotype should be checked to document genotype (McAleer and Kaplan, 2001). In severe cases of hypospadias where penile size is difficult to assess secondary to severe chordee, an hCG stimulation will assess the gonadal axis and confirm an intact AR by eliciting penile growth.

B. Micropenis

A penis measuring less than 2.5 cm in stretched penile length without hypospadias in a full-term male is defined as **micropenis** (Figure 43–23; see also Table 43–4). Micropenis can be caused by multiple etiologies; the most common one is fetal testosterone deficiency followed by partial defects in the AR or 5α-reductase enzyme (Table 43–7). Fetal testosterone synthesis can be divided into two categories: (1) primary testicular failure (Leydig cell) and (2) central failure. Central failure can result from congenital hypopituitarism or isolated gonadotropin deficiency. Patients with decreased fetal testosterone production either from (Fallat and Donahoe, 2006) Leydig cell failure or lack of Leydig cell stimulation from gonadotropin deficiency respond to treatment with supplementary testosterone enanthate intramuscular injections 25–50 mg each month for 3 consecutive months.



▲ **Figure 43–23.** Micropenis. Normal corporeal bodies are palpable within the foreskin. The urethral meatus is at a terminal position within the glans. Stretched penile length is <2.5 cm in this full-term infant.

Table 43–7. Etiologies of micropenis.

- **Deficient testosterone secretion**
  - Hypogonadotropic hypogonadism
    - Kallmann syndrome
    - Prader–Willi syndrome
    - Laurence–Moon syndrome
    - Bardet–Biedl syndrome
    - Rudd syndrome
  - Primary hypogonadism (“bum gonads”)
    - Anorchia
    - Klinefelter syndrome
    - Gonadal dysgenesis (partial)
    - LH receptor defects (partial)
    - Noonan syndrome
    - Trisomy 21
    - Robinow syndrome
    - Bardet–Biedl syndrome
    - Laurence–Moon syndrome
    - Testosterone synthesis defects (partial)
- **Defects in testosterone action**
  - Androgen receptor defects (partial)
  - 5α-Reductase deficiency
  - Growth hormone/insulin growth factor 1 deficiency
  - Fetal hydantoin syndrome
- **Developmental anomalies**
  - Aphallia
  - Cloacal exstrophy
  - Iatrogenic injuries
    - Circumcision
    - Trauma

Long-term outcomes of patients with micropenis have documented that final adult penile length is normal for >90% of patients treated with multiple short courses of testosterone enanthate. In addition, patients with micropenis identified with the male gender had normal erections, ejaculation, and orgasm. In rare patient who does not respond to testosterone stimulation, gender conversion to female had been advocated in the past. Presently, gender conversion would not be considered, based solely on the small phallus size.

Reassignment to the female gender with removal of the gonads and feminizing genitoplasty in patients with penile agenesis, iatrogenic penile amputation, or circumcision injury is historical treatment. In complete penile agenesis, the testicles are normal, corporeal bodies are absent, and the urethra opens into the anterior rectum or perineum. These patients have normal prenatal androgen levels, and hence, the brain has received signals for male gender identity (Wisniewski et al, 2001). The same is true for the rare patient who has a severe penile injury during circumcision. As in micropenis, gender conversion would now not be considered, based solely on the absence or small size of the phallus. Penile reconstruction, although not technically ideal, may provide the best overall outcome.

C. Cloacal and Exstrophy Anomalies

In the distant past, patients with the most severe and rare form of lower abdominal congenital malformation, cloacal exstrophy (incidence of 1 in 200,000 live births), were usually left to die. Significant problems associated with surgical reconstruction of cloacal exstrophy include omphalocele; numerous gastrointestinal anomalies such as short gut, malrotation, duplication, duodenal atresia, and Meckel's diverticulum; and significant genitourinary anomalies such as separate bladder halves, upper tract renal anomalies, and bifid genitalia. Patients with cloacal exstrophy can also have neurologic and orthopedic anomalies such as tethered cord, myelomeningocele, lower extremity paralysis, clubfoot, and hip dislocation.

Historically, newborn males with cloacal exstrophy (Figure 43–24) were often gender-converted to female as a result of inadequate genital development and the poor prognosis for surgically developing a normal male phenotype. In rearing genetic males as females, although the surgical reconstruction can match the assigned female phenotype, a new set of issues was created, such as the need for hormonal replacement with estrogen during adolescence and the issue of a nonmenstruating infertile female. In addition, the fetal and neonatal androgen imprinting on the brain does not seem to be reversible.

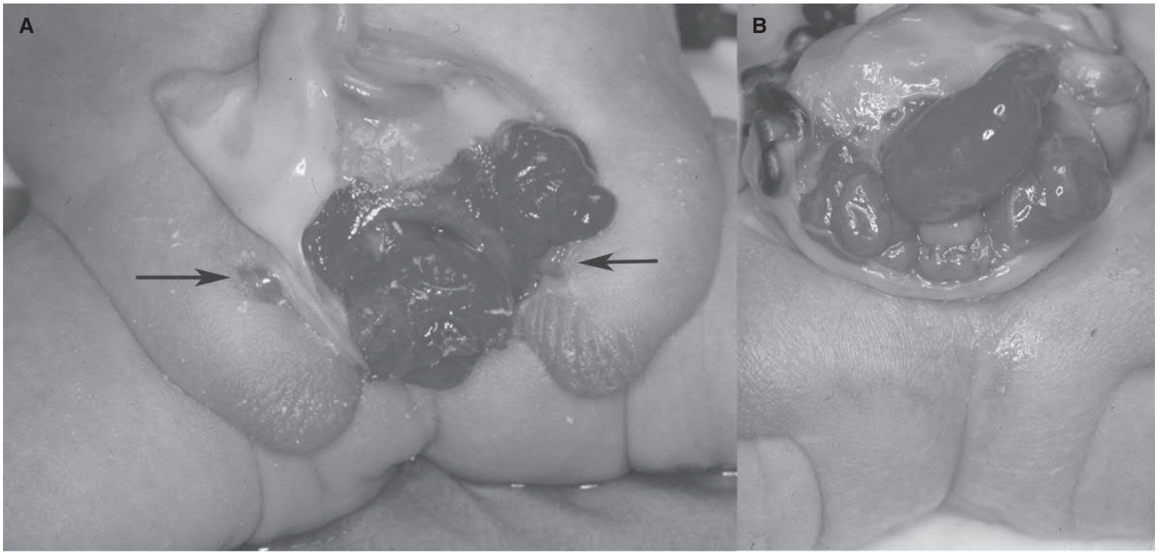
Because some of these XY, gender-converted females have self-reassigned their sex during adolescence to coincide with their genetic karyotype, there has been reevaluation of the practice of rearing genetic males as females. With the exact determinates of sexual identity not completely defined, a pragmatic approach is to delay any irreversible surgery such as orchiectomy or phallic removal/reduction in these patients. With modern surgical techniques and a multidisciplinary approach to their care, children with this complex disorder can have a normal *sexual* identity.

SURGICAL MANAGEMENT OF DSD

The surgical management of patients with DSD is undergoing a reevaluation (Mouriquand et al, 2016). The determination of a patient's *sexual* identity is strongly influenced by the genetic karyotype and steroid/androgen action on the developing brain. The environmental and social impacts are certainly important but presently seem to have a less dominating influence (Suorsa et al, 2015).

We would advocate surgical management of patients with DSD when the diagnosis is clearly established and the long-term outcome for the diagnosis is favorable. Examples include the majority of patients with DSD such as CAH (female sex of rearing) and mixed gonadal dysgenesis (male sex of rearing) (Nordenstrom et al, 2010; Merke and Poppas, 2013). Examples where long-term outcome for sexual identity is not established include ovotesticular syndrome and severe partial androgen insensitivity. Surgery falls into five categories: (1) diagnostic/biopsy, (2) gonadectomy and removal of inappropriate Müllerian structures, (3) clitoral reduction, (4) vaginoplasty, and (5) phallic reconstruction.

Diagnostic techniques have improved with the widespread use of laparoscopy to assess the morphology of the



▲ **Figure 43–24.** ***A:*** Male with cloacal exstrophy. ***B:*** Female with cloacal exstrophy. In the male, note the split scrotal appearance and the small hemiphallus (*arrow*). In the female, the clitoral bodies/genitalia are not visible.

internal genital structures. Laparoscopic techniques allow the gonads and associated structures to be visualized and in certain cases permit the surgeon to take a biopsy specimen without the need for an open incision. Once the diagnosis is established, it is possible to remove an inappropriate gonad, Müllerian remnant, or both via laparoscopic techniques.

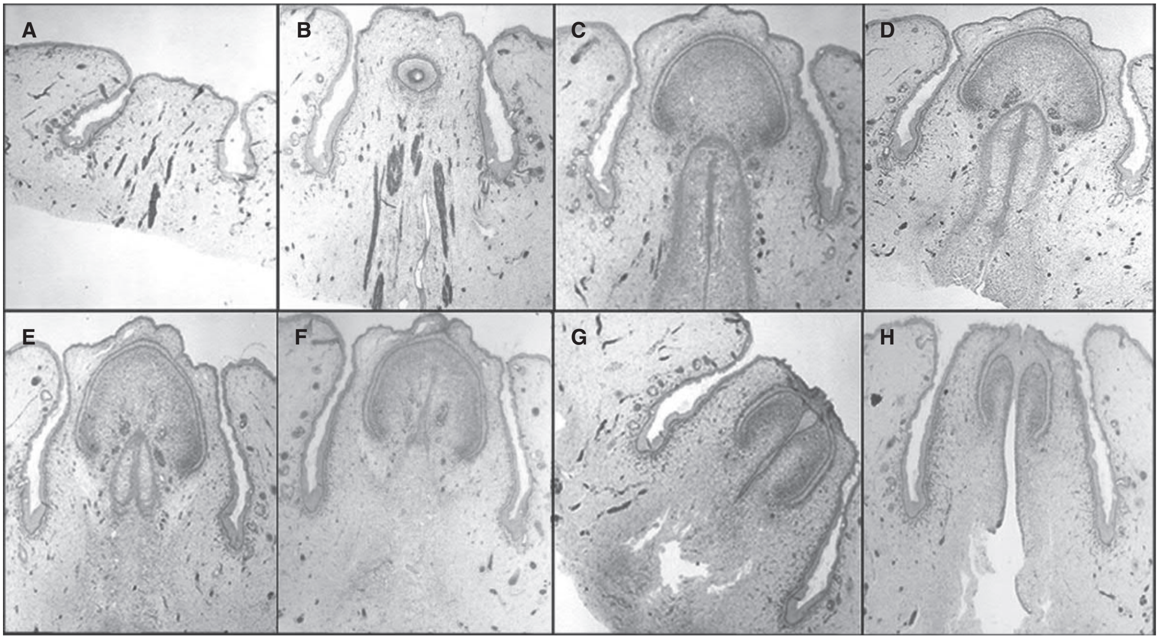
Clitoroplasty

Clitoroplasty remains a controversial topic. No studies exist to clearly document whether androgen stimulation resulting in a large clitoris requires reduction or can be left intact. Clearly, surgery on the clitoral structures can result in nerve damage and removal of erectile tissue.

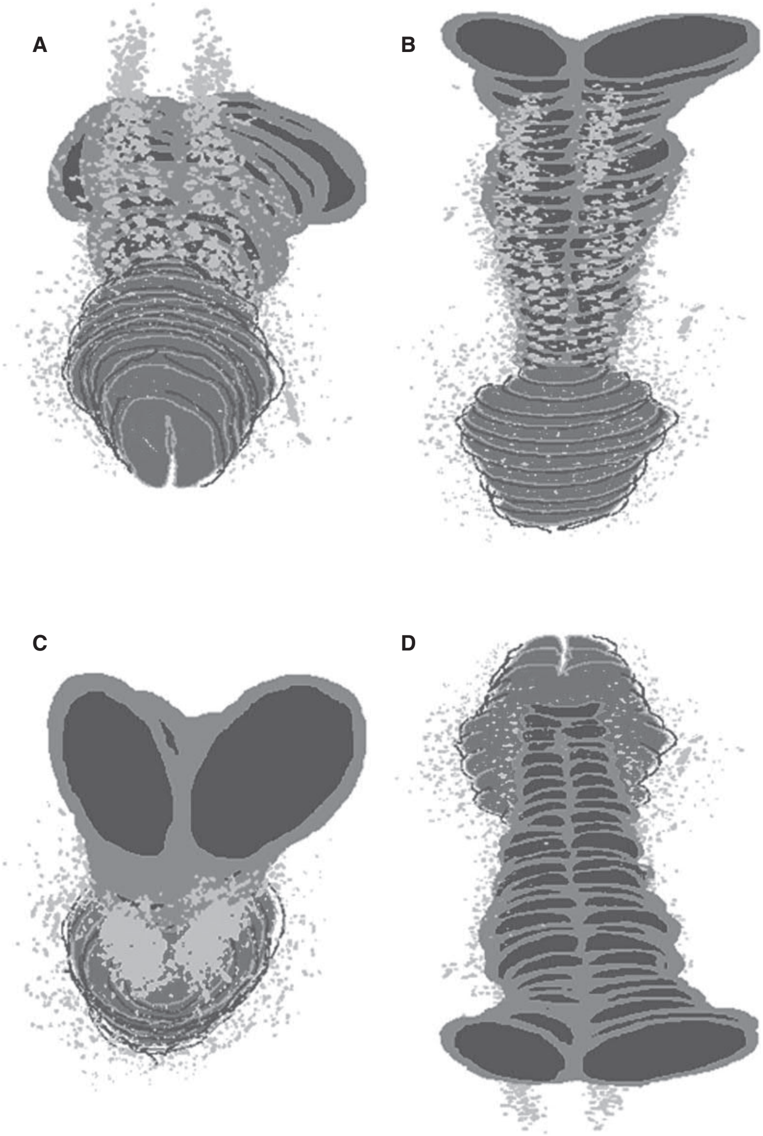
Historically, the enlarged clitoris/phallic structure has been managed by amputation (Gross and Crigler, 1966). Subsequently, more refined techniques such as recession clitoroplasty were developed where the entire clitoral organ was preserved by imbricating and burying the proximal corporeal shaft and excess glans clitoris. The disadvantage of the clitoral recession procedures may not become apparent until puberty, when the recessed corporeal bodies become enlarged and painful during sexual stimulation. This leads to the need for a procedure involving subtotal resection of the shaft of the clitoris with preservation of the glans.

In cases where clitoroplasty is performed, the goal is to recreate the normal female anatomy. Presently, more conservative procedures have been employed to preserve both the sensory and cosmetic aspects of the clitoris. An understanding of normal female anatomy has benefited the design of reconstructive surgery in patients with CAH (Figures 43–25 and 42–26) (Baskin et al, 1999). A contemporary reduction clitoroplasty is based on anatomical observations from fetal anatomical dissections (Wang and Poppas, 2016). Presently, the tunica of the corporeal body can be preserved to spare as much of the dorsal nerve as possible. The concept of lifting the dorsal nerve off the tunica at the 11 and 1 o'clock positions seems inconsistent with the fact that the nerves fan out extensively around the dorsal and lateral aspects of the clitoral body.

A second issue is the removal of erectile tissue. In severe cases of masculinization of the genitalia (Prader V), consideration may be given to reduce the amount of erectile tissue. Previously, standard treatment was to amputate the erectile body of the clitoris at the pubic arch, leaving each crural body and the neurovascular bundle with a strip of dorsal tunica. The long-term effects of removing this erectile tissue on sexual function are unknown. In contrast, leaving too much erectile tissue has been reported to cause pain in patients at the time of puberty. This, however, may be from fixing the corporeal tissue to the pubic bone, a practice that is no longer advocated. A compromise is to incise the erectile body on the ventral surface at the



▲ **Figure 43–25.** Normal human fetal clitoris at 24 weeks' gestation (40×) immunostained with the neuronal marker S-100 (*dark brown stain*). ***A:*** Clitoral hood, labia minora, and majora. ***B:*** Nerves on top of the erectile body and top of glans clitoris. ***C–E:*** Glans clitoris and erectile bodies. ***F–G:*** Lower part of glans clitoris with midline cleft. ***H:*** End of glans clitoris and vaginal introitus.



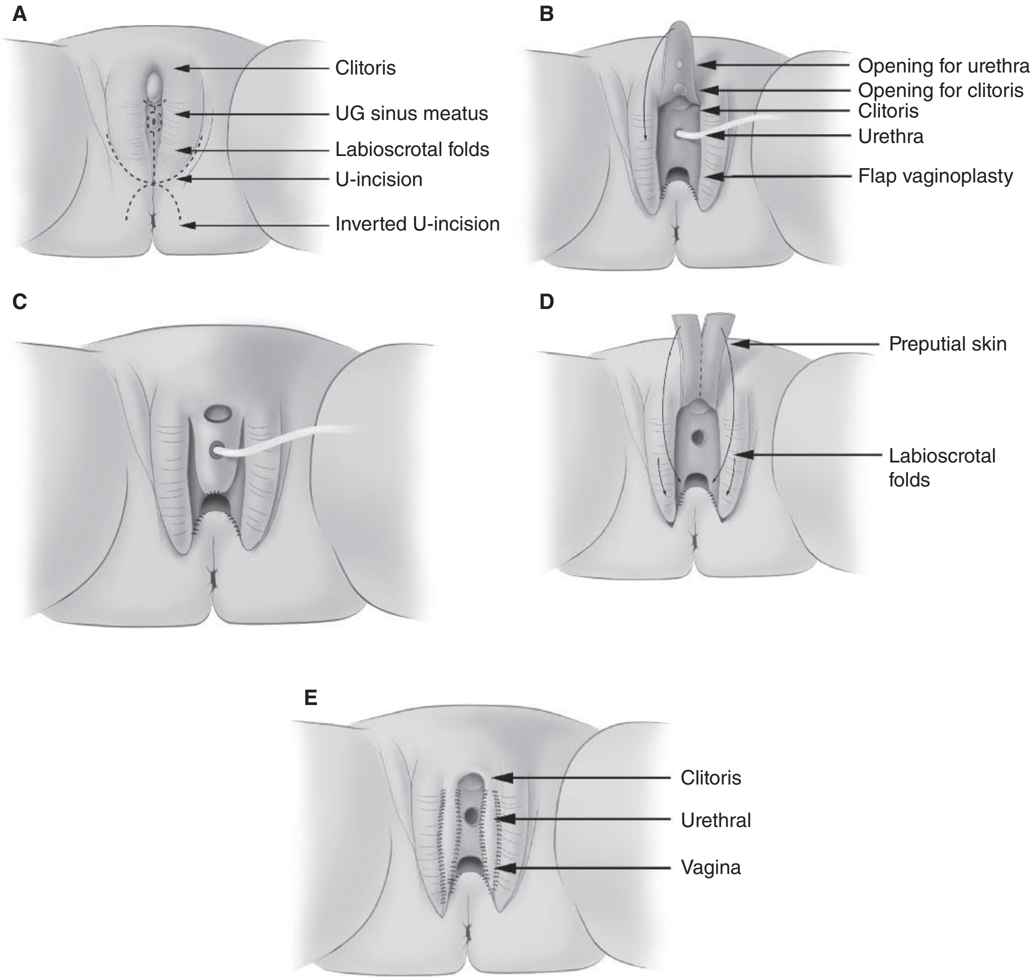
▲ **Figure 43–26.** Normal human fetal clitoris, 24 weeks' gestation. Four views of a computer-generated three-dimensional reconstruction (***A:*** top; ***B:*** bottom; ***C:*** back/top; ***D:*** bottom). Note the pathway of the nerves (red) with a paucity of nerves on the bottom of the clitoris as well as in the top midline. Glans = green; crural body = yellow; tunica of crural body = purple.

6 o'clock position away from the nerves and remove erectile tissue within the tunica to reduce the size of the erectile body, thereby preserving some erectile tissue and the nerves of the clitoris.

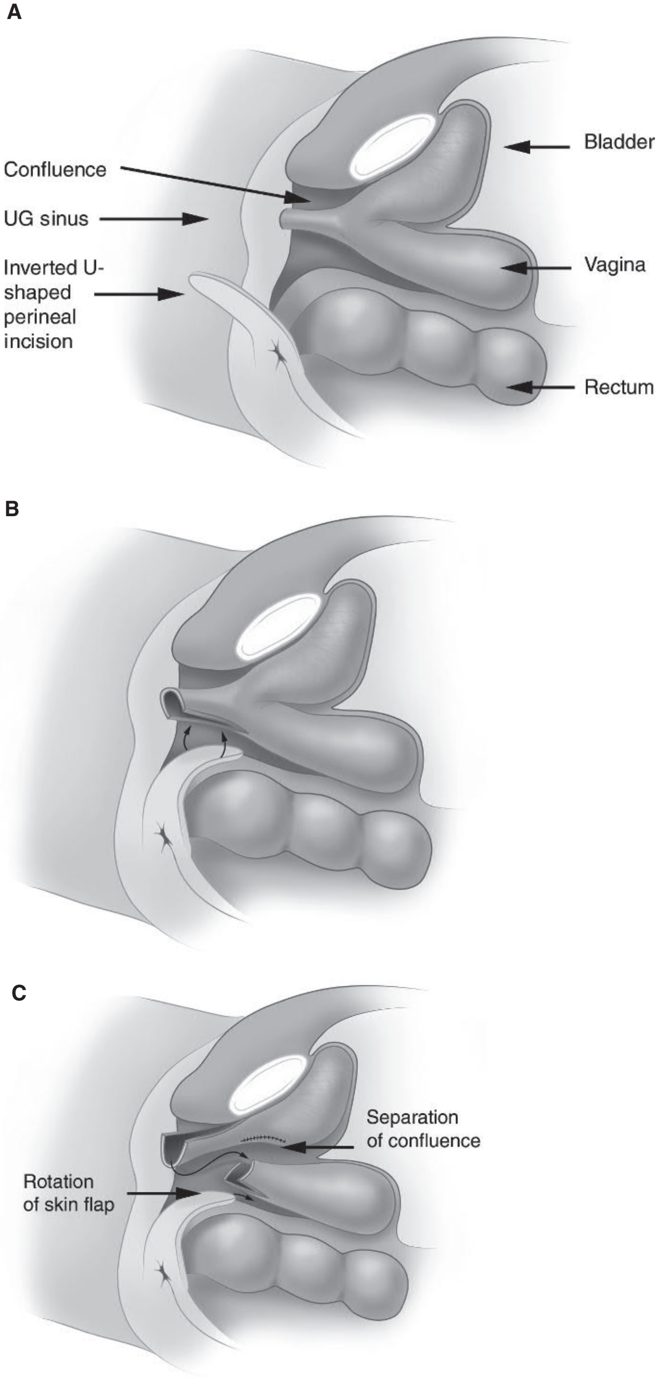
▶ Vaginoplasty

The timing of vaginoplasty is also a controversial issue in genital reconstruction. The presence of a vagina is not necessary until puberty and initially only to allow the passage of menstrual fluids. Later the vagina is necessary for vaginal penetration, fertility, and, in most females, a healthy female *sexual* identity. This may not be the case for all females; for example, a woman with a small vagina and a female *sexual* identity with a female sexual preference may not desire a larger vagina. In patients with absent Müllerian structures (specifically a functional uterus) who have a female *sexual* identity, menstruation is not an issue and timing of vaginoplasty can be driven by the patient's wishes and motivation. In patients with a common urogenital sinus and hidden vagina, there are advantages and disadvantages of early surgery in the first year of life versus late surgery prior to puberty (Farkas et al, 2001). The advantage of early vaginoplasty is the closeness of the vagina to the perineum and the early timing of genital surgery recommended by the American Academy of Pediatrics Task Force on Genital Surgery. The disadvantages are the smallness of the structures and that secondary surgery at the time of puberty may be necessary to correct vaginal stenosis. In contrast, delaying surgery has the advantages of operating on larger structures and the possibility that the patient can perform postoperative vaginal dilation to prevent stenosis (Hensle et al, 2006).

The type of vaginoplasty depends on the level of masculinization (Kalfa et al, 2008). For low-urogenital-sinus anomalies, a flap vaginoplasty will usually allow for an adequate introitus with separation of the urethra and vagina (Figure 43–27). For high-urogenital-sinus anomalies, partial urogenital mobilization and use of the elongated common urogenital sinus as an anterior vaginal flap may be necessary (Figure 43–28)



▲ **Figure 43–27.** Female external genitalia reconstruction in patients with a low confluence using a flap vaginoplasty. ***A:*** Surgical schematic of the perineum in patients with common urogenital sinus. ***B:*** The anterior flap for the vagina can be created using the phallic skin or the distal portion of the urogenital sinus. Two openings are created in the midline of the preputial skin flap to accommodate the clitoris and urethra. The preputial skin flap is then brought down and sutured to the anterior wall of the vagina. ***C:*** The completed repair. ***D:*** Alternatively, the preputial skin can be split in the midline and used for reconstruction of the vaginal introitus and the anterior vaginal wall. ***E:*** The completed repair.



▲ **Figure 43–28.** Partial urogenital mobilization for high urogenital sinus. ***A:*** The urogenital (UG) sinus is separated from the rectum posteriorly and the pubic bone anteriorly. ***B:*** The posterior skin flap (*arrows*) is assessed for length to reach the vagina. ***C:*** The confluence of the vagina and urethra (*arrow*) is separated.

(Rink and Cain, 2008). In cases of an absent vagina or a very short vagina, substitution vaginoplasty with bowel or skin grafting may be required (Thomas and Brock, 2007). More recently autologous buccal mucosa has been successfully for used vaginal reconstruction (Samuelson and Baker, 2006).

Phallic Reconstruction

Phallic reconstruction is a formidable task. Nevertheless, it is critical that reconstructive efforts continue in this area, especially for patients with penile agenesis or iatrogenic injuries and a XY genotype and functional AR. Several techniques have been devised, such as free microanastomosis, innervated radial forearm flaps, tubed abdominal flaps with a penile prosthesis, and rectus abdominis myocutaneous flaps. In the free radial forearm flap, the pudendal nerve is anastomosed to the lateral cutaneous nerve of the forearm. The radial artery and vein are anastomosed to the inferior epigastrics, the internal pudendals, or the femoral vessels. The major complications with these procedures are fistula, prosthesis erosion, and poor sensation. The technical nuances of microvascular anastomosis require that these procedures be performed in adolescence and adulthood. The psychological implications of relatively late reconstruction have not been determined. More recently, a technique for creating a neonatal phallus from abdominal wall tissue has been described by De Castro et al (2007). Early results are encouraging, but longer follow-up and the need for revision at the time of puberty will need to be determined. With newer tissue engineering techniques, better phallic reconstruction procedures may be on the horizon.

BIBLIOGRAPHY

Auchus RJ, Witchel SF, Leight KR, Aisenberg J, Azziz R, Bachega TA, et al: Guidelines for the development of comprehensive care centers for congenital adrenal hyperplasia: Guidance from the CARES Foundation Initiative. Int J Pediatr Endocrinol 2010;275213.

Baskin LS et al: Anatomical studies of hypospadias. J Urol 1998;160 (3 Pt 2):1108–1115.

Baskin LS et al: Anatomical studies of the human clitoris. J Urol 1999;162(3 Pt 2):1015–1020.

Baskin LS et al: Hypospadias and endocrine disruption: Is there a connection? Environ Health Perspect 2001;109(11):1175–1183.

Baskin LS, Ebbers MB: Hypospadias: Anatomy, etiology, and technique. J Pediatr Surg 2006;41(3):463–472.

Birnbacher R et al: Gender identity reversal in an adolescent with mixed gonadal dysgenesis. J Pediatr Endocrinol Metab 1999;12(5):687–690.

Camurdan AD et al: Current stretched penile length: Cross-sectional study of 1040 healthy Turkish children aged 0 to 5 years. Urology 2007;70(3):572–575.

Chang HJ et al: The phenotype of 45,X/46,XY mosaicism: An analysis of 92 prenatally diagnosed cases. Am J Hum Genet 1990;46(1):156–167.

Conte FA, Grumbach MM: Disorders of sexual determination and differentiation. Chapter 15. In: Gardner DG, Shoback D (eds): Greenspan's Basic and Clinical Endocrinology. 8th ed. McGraw-Hill, New York, 2007, pp. 562–610.

Cools M, Looijenga LH, Wolffenbuttel KP, T'Sjoen G.: Managing the risk of germ cell tumourigenesis in disorders of sex development patients. Endocr Dev 2014;27:185–196 (doi: 10.1159/000363642).

Daaboul J, Frader J: Ethics and the management of the patient with intersex: A middle way. J Pediatr Endocrinol Metab 2001;14(9): 1575–1583.

De Castro R et al: Phalloplasty and urethroplasty in children with penile agenesis: Preliminary report. J Urol 2007;177(3):1112–1116; discussion 1117.

Fallat ME, Donahoe PK: Intersex genetic anomalies with malignant potential. Curr Opin Pediatr 2006;18(3):305–311.

Farkas A et al: 1-Stage feminizing genitoplasty: 8 years of experience with 49 cases. J Urol 2001;165(6 Pt 2):2341–2346.

Griffin J et al: The androgen resistance syndromes: Steroid 5 alpha-reductase deficiency, testicular feminization and related disorders. In: Scriver C (ed): The Metabolic and Molecular Bases of Inherited Disease, Vol. 3. McGraw-Hill, Philadelphia, 1995, pp. 2967–2998.

Gross R, Crigler R: Clitorectomy for sexual abnormalities, indications and techniques. J Surg 1966;59:300–308.

Hensle TW et al: Sexual function following bowel vaginoplasty. J Urol 2006;175(6):2283–2286.

Hughes IA: Congenital adrenal hyperplasia: A lifelong disorder. Horm Res 2007;68(Suppl 5):84–89.

Jirasek J et al: The relationship between the development of gonads and external genitals in human fetuses. Am J Obstet Gynecol 1968;101:830.

Kalfa N, Liu B, Cao M, Vilella M, Hsieh M, Baskin LS: 3-dimensional neuroanatomy of the human fetal pelvis: Anatomical support for partial urogenital mobilization in the treatment of urogenital sinus. J Urol 2008;180(4 Suppl):1709–1714; discussion 1714–1715.

Kathrins M, Kolon TF: Malignancy in disorders of sex development. Transl Androl Urol 2016;5(5):794–798.

Kim KS et al: Expression of the androgen receptor and 5 alpha-reductase type 2 in the developing human fetal penis and urethra. Cell Tissue Res 2002;307(2):145–153.

Kurzrock E et al: Ontogeny of the male urethra: Theory of endodermal differentiation. Differentiation 1999;64:115–122.

Lee PA et al: Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics 2006; 118(2):e488–e500.

Levin HS: Tumors of the testis in intersex syndromes. Urol Clin North Am 2000;27(3):543–551, x.

Li Y, Sinclair A, Cao M, Shen J, Choudhry S, Botta S, Cunha G, Baskin L: Canalization of the urethral plate precedes fusion of the urethral folds during male penile urethral development: The double zipper hypothesis. J Urol 2015;193(4):1353–1359.

Loscalzo ML: Turner syndrome. Pediatr Rev 2008;29(7):219–227.

McAleer IM, Kaplan GW: Is routine karyotyping necessary in the evaluation of hypospadias and cryptorchidism? J Urol 2001;165(6 Pt 1): 2029–2031; discussion 2031–2032.

Merke DP, Poppas DP: Management of adolescents with congenital adrenal hyperplasia. Lancet Diabetes Endocrinol 2013;1(4): 341–352.

Mouriquand PD, Gorduza DB, Gay CL, Meyer-Bahlburg HF, Baker L, Baskin LS, et al: Surgery in disorders of sex development (DSD) with a gender issue: If (why), when, and how? J Pediatr Urol 2016;12(3):139–149.

Nordenstrom A, Frisen L, Falhammar H, Filipsson H, Holmdahl G, Janson PO et al: (2010). Sexual function and surgical outcome in women with congenital adrenal hyperplasia due to CYP21A2 deficiency: Clinical perspective and the patients' perception. J Clin Endocrinol Metab 2010;95(8):3633–3640.

Miller W: Prenatal treatment of congenital adrenal hyperplasia—a promising experimental therapy of unproven safety. Trends Endocrinol Metab 1998;9:290–293.

Morland I: Management of intersex. Lancet 2001;358(9298): 2085–2086.

Oakes MB et al: Complete androgen insensitivity syndrome—a review. J Pediatr Adolesc Gynecol 2008;21(6):305–310.

Overland M, Li Y, Cao M, Shen J, Yue X, Botta S, et al: Canalization of the vestibular plate in the absence of urethral fusion characterizes development of the human clitoris: The single zipper hypothesis. J Urol 2016;195(4 Pt 2):1275–1283.

Rey RA et al: Evaluation of gonadal function in 107 intersex patients by means of serum antimullerian hormone measurement. J Clin Endocrinol Metab 1999;84(2):627–631.

Rink RC, Cain MP: Urogenital mobilization for urogenital sinus repair. BJU Int 2008;102(9):1182–1197.

Samuelson ML, Baker LA: Autologous buccal mucosa vulvovaginoplasty for high urogenital sinus. J Pediatr Urol 2006;2(5):486–488.

Speiser PW: Prenatal and neonatal diagnosis and treatment of congenital adrenal hyperplasia. Horm Res 2007;68(Suppl 5):90–92.

Suorsa KI, Mullins AJ, Tackett AP, Scott Reyes KJ, Austin P, Baskin L, et al: Characterizing early psychosocial functioning of parents of children with moderate to severe genital ambiguity due to disorders of sex development. J Urol 2015;194(6):1737–1742.

Thomas JC, Brock JW III: Vaginal substitution: Attempts to create the ideal replacement. J Urol 2007;178(5):1855–1859.

Wilson JD et al: The hormonal control of sexual development. Science 1981;211(4488):1278–1284.

Wilson JD et al: Steroid 5 alpha-reductase 2 deficiency. Endocr Rev 1993;14(5):577–593.

Wisniewski AB et al: Complete androgen insensitivity syndrome: Long-term medical, surgical, and psychosexual outcome. J Clin Endocrinol Metab 2000;85(8):2664–2669.

Wisniewski AB et al: Congenital micropenis: Long-term medical, surgical and psychosexual follow-up of individuals raised male or female. Horm Res 2001;56(1–2):3–11.

Wolffenbuttel KP, Hersmus R, Stoop H, Biermann K, Hoebeke P, Cools M, Looijenga LH: Gonadal dysgenesis in disorders of sex development: Diagnosis and surgical management. J Pediatr Urol 2016 (pii: S1477-5131(16)30274-1; doi: 10.1016/j.jpurol.2016.08.015).

Woodhouse CR: Prospects for fertility in patients born with genitourinary anomalies. J Urol 2001;165(6 Pt 2):2354–2360.

Zucker KJ: Re: Androgen imprinting of the brain in animal models and humans with intersex disorders: Review and recommendations. J Urol 2003;169(6):2306.

44

Male Infertility

Thomas J. Walsh, MD, MS; &
James F. Smith, MD, MS

Infertility is defined as the failure to conceive despite one year of regular unprotected intercourse. Approximately 15% of couples will experience infertility, and of these, 20% will have a male factor that is solely responsible; male factors will contribute in an additional 30% of cases. Generally, male infertility is identified by abnormalities on a semen analysis; however, other issues can contribute to infertility despite normal semen.

The causes of male infertility are widely varied and are best evaluated by a urologist. Some causes of male infertility can be identified and reversed or improved with *specific* surgery or medication, while other causes can be identified but not reversed. Occasionally the underlying cause of infertility or an abnormal semen analysis cannot be identified, in which case it is termed **idiopathic**. These cases may be amenable to *empiric* treatment to improve the chances of conception.

MALE REPRODUCTIVE PHYSIOLOGY

THE HYPOTHALAMIC–PITUITARY–GONADAL AXIS

The hypothalamic–pituitary–gonadal (HPG) axis plays a critical role in both the endocrine (testosterone production) and exocrine (sperm production) functions of the testes. Several endocrine concepts must be reviewed.

A. Hormone Classification (Figure 44–1)

Both peptide and steroid hormones are required for communication in the reproductive axis. Peptide hormones are small secretory proteins that bind receptors on the cell surface membrane and induce a series of intracellular events. Hormone signals are transduced by second-messenger pathways whose actions culminate in protein phosphorylation that alters cell function. The key peptide hormones of the HPG axis are luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Steroid hormones are derived from cholesterol and unlike peptide hormones are not stored in secretory granules, and as a result their secretion is limited by the rate of production. Since they are lipophilic, steroid hormones are generally cell membrane permeable. In plasma, steroid hormones are largely bound to serum proteins, with only a small “free” component available to diffuse into the intracellular space and bind receptors. Once bound to an intracellular receptor, steroids are translocated to deoxyribonucleic acid (DNA) recognition sites within the nucleus where they act by regulating the transcription of target genes. The key steroid hormones of the HPG axis are testosterone (T) and estradiol (E2).

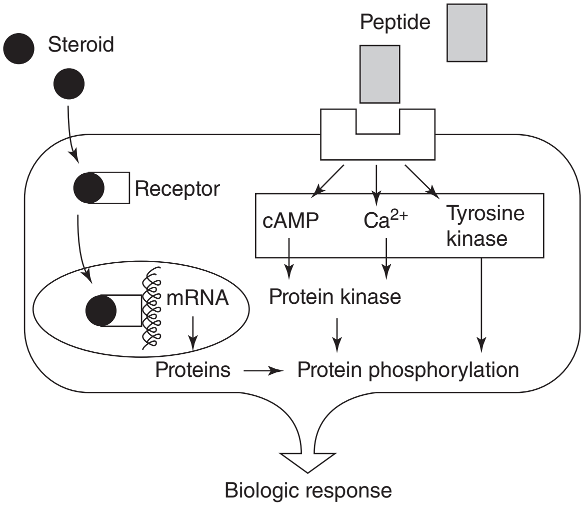
B. Feedback Loops

Normal endocrine and exocrine function of the testes depends on the orchestrated action of numerous hormones. Positive and negative feedback are the principal mechanism through which hormonal regulation occurs. By this mechanism, a hormone can regulate the synthesis and action of itself or of another hormone. Further coordination is provided by hormone action at multiple sites and through multiple responses. In the HPG axis, negative feedback is responsible for minimizing hormonal perturbations and maintaining homeostasis.

▶ Anatomy of the Hypothalamic–Pituitary–Gonadal Axis (Figure 44–2)

A. Hypothalamus

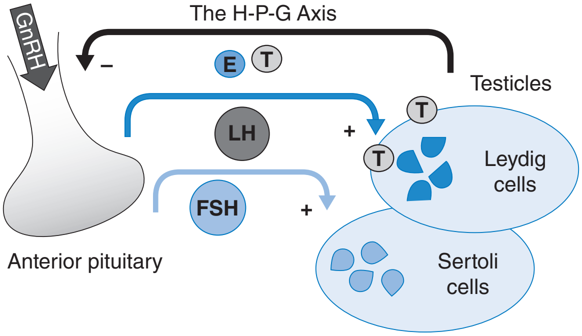
The hypothalamus receives and integrates neuronal input from the amygdala, thalamus, pons, retina, and cortex. The pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus causes the cyclical secretion of pituitary and gonadal hormones. It is anatomically linked to the pituitary gland by both a portal vascular system and neuronal pathways, thus avoiding the systemic circulation. GnRH is a 10-amino acid peptide secreted from neurons in



▲ **Figure 44–1.** Two kinds of hormone classes mediate intercellular communication in the reproductive hormone axis: peptide and steroid.

the preoptic and arcuate nuclei of the hypothalamus. Once secreted into the pituitary portal circulation, GnRH has a half-life of approximately 5–7 minutes, almost entirely removed on the first pass through the pituitary where it stimulates the production and secretion of FSH and LH.

Secretion of GnRH is highly responsive to a variety of hormonal and pharmacologic inputs (Table 44–1) and may also be impacted by drugs, medications, stress, exercise, and diet. The pulse frequency of GnRH secretion varies from once or twice in 24 hours to every hour and can be abolished by the administration of GnRH agonists.



▲ **Figure 44–2.** Major components of the HPG axis and recognized hormone feedback pathways. (FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; PRL = prolactin; T = testosterone; + = positive feedback; – = negative feedback.)

Table 44–1. Substances that modulate GnRH secretion.

GnRH modulator	Type of feedback	Examples
Opioids	Negative/inhibitory	β-Endorphin
Catecholamines	Variable	Dopamine
Peptide hormones	Negative/inhibitory	FSH, LH
Sex steroids	Negative/inhibitory	Testosterone
Prostaglandins	Positive/stimulatory	PGE_2

FSH = follicle-stimulating hormone; LH = luteinizing hormone; PGE_2 = prostaglandin E_2.

B. Anterior Pituitary

The anterior pituitary gland is located within the sella turcica of the skull and secretes a series of peptide hormones, including the gonadotropins. GnRH stimulates both production and secretion of FSH and LH by a calcium flux-dependent mechanism. The sensitivity of the pituitary gonadotrophs for GnRH varies with patient age and hormonal status.

Both LH and FSH are glycoproteins composed of alpha and beta subunits, each encoded by separate genes. The alpha subunits of each hormone are identical and are similar to that of all other pituitary hormones; thus, their unique biologic activities are conferred by the beta subunits. Pulsatile secretion of LH varies from 8 to 16 pulses per day with variation in amplitude by one- to threefold. The pulse patterns reflect GnRH release and are regulated by androgens and estrogens through negative feedback. Pulsatile secretion of FSH occurs approximately every 1.5 hours and also demonstrates amplitude variation. Because FSH secretion is smaller in amplitude and has a longer serum half-life, its responsiveness to GnRH is more difficult to measure. In addition to its regulation by serum steroid hormones, FSH appears to have unique and independent responsiveness to the gonadal proteins inhibin and activin.

In the testis, LH stimulates steroidogenesis within Leydig cells by inducing the mitochondrial conversion of cholesterol to pregnenolone and testosterone. FSH binds to Sertoli cells and spermatogonial membranes within the testis and is the major stimulator of seminiferous tubule growth during development and initiates spermatogenesis at puberty. In adults, the major physiologic role of FSH is to maintain quantitatively normal spermatogenesis. Both FSH and LH bind cell surface receptors that activate adenylate cyclase and cause increases in intracellular cyclic adenosine monophosphate (cAMP).

Prolactin (PRL) is also produced and secreted by the anterior pituitary and can impact both the HPG axis and fertility. Prolactin is a large (23 kDa), globular protein that potentiates milk production and lactation during pregnancy. The role of prolactin in men is poorly understood, but it may increase the concentration of LH receptors on the Leydig cell and may help sustain high intratesticular testosterone levels. It may also potentiate the effects of androgens on the growth and secretions of male accessory sex glands. Normal prolactin levels may be important in the maintenance of libido. Elevated prolactin appears to abolish gonadotropin pulsatility by interfering with episodic GnRH release. A markedly elevated prolactin may be evidence of a PRL secreting adenoma of the pituitary (prolactinoma) and requires further evaluation.

C. The Testis

Normal male reproduction requires that the testes have both endocrine and exocrine function. Both of these functions are under the control of the HPG axis. Steroidogenesis occurs in the interstitial compartment, where Leydig cells reside. Spermatogenesis occurs in the seminiferous tubules with the support of Sertoli cells.

1. Endocrine testis—Men normally produce approximately 5 g of testosterone per day. Approximately 2% of testosterone circulates “free” in the serum and is considered the biologically active fraction. The remaining testosterone is bound to sex hormone-binding globulin (SHBG) and, to a slightly lesser extent, albumin within the blood. Several conditions can alter SHBG levels within the blood, thus changing the amount of free or bioavailable testosterone available for tissues. Obesity, diabetes, and chronic glucocorticoid use leads to decreased production of SHBG and therefore a decrease in total testosterone despite a normal free fraction. Conversely, hypothyroidism, cirrhosis of the liver, chronic anticonvulsive therapy, and aging all lead to increased SHBG production and therefore an elevation of total testosterone level.

Testosterone is metabolized into two primary metabolites in target tissues: (1) dihydrotestosterone (DHT) by the enzyme 5α-reductase and (2) estradiol by the enzyme aromatase. DHT is a more potent androgen than testosterone, and in many tissues the conversion of testosterone to DHT is required for androgen action. While aromatase is present in many tissues, adipocytes play a significant role in the aromatization of testosterone to estradiol. Estradiol has a pivotal role in the regulation of the HPG axis. Testosterone, through its conversion to estradiol, is the primary regulator of its own production through negative feedback on the HPG axis.

2. Exocrine testis—FSH acts primarily on Sertoli cells within the seminiferous tubules to induce the production of numerous proteins necessary for spermatogenesis, including androgen-binding protein, transferrin, lactate, ceruloplasmin, clusterin, plasminogen activator, prostaglandins, and several growth factors. Through these actions, seminiferous tubule growth is stimulated during development and sperm production is initiated during puberty and maintained in adulthood.

3. Inhibin and activin—Inhibin is a 32-kDa protein derived from Sertoli cells that inhibits FSH release from the anterior pituitary. Inhibin production is stimulated by FSH and acts by negative feedback at the pituitary and hypothalamus. Activin, a peptide hormone with structural homology to transforming growth factor-beta (TGFβ), appears to stimulate FSH secretion through its action on the hypothalamus and pituitary. Activin receptors are found in a host of extragonadal tissues, suggesting that this hormone may have a variety of growth factor or regulatory roles in the body.

SPERMATOGENESIS

Spermatogenesis is a complex process during which primitive, multipotent stem cells divide to either renew themselves or produce daughter cells (mitosis) that further divide (meiosis) and mature to become spermatozoa. These processes occur within the seminiferous tubules of the testis, and 80–90% of testis volume is made up of the seminiferous tubules and germ cells at various developmental stages. Thus, it is not surprising that testicular hypotrophy and atrophy are strongly correlated to semen parameters.

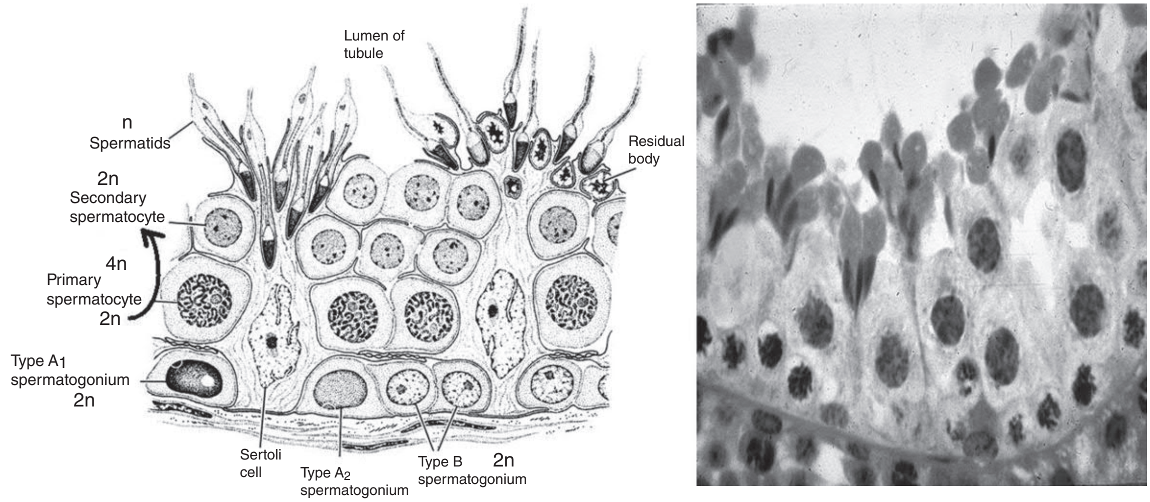
▶ Sertoli Cells

Sertoli cells line the seminiferous tubules and are linked by tight junctions. These junctional complexes divide the seminiferous tubule space into basal (basement membrane) and adluminal (lumen) compartments and form the basis for the blood–testis barrier. As a result of this tight junction barrier, spermatogenesis occurs in an immunologically privileged site. Sanctuary from the immune system is critical given that immune recognition develops during the first year of life and spermatozoa are produced at puberty and therefore contain foreign antigens.

Sertoli cells foster spermatogenesis and participate in germ cell phagocytosis. FSH binding to high-affinity FSH receptors on Sertoli cells induces production and secretion of androgen-binding protein. Within the luminal fluid, this protein binds testosterone leading to levels 20–50 times that found in serum. Other regulatory effects of Sertoli cells include the production of inhibin and ligand–receptor complexes, such as c-*kit* and kit ligand.

▶ Germ Cells

Germ cells are highly ordered within the cross section of the seminiferous tubules. Spermatogonia sit directly on the basement membrane and are followed by primary spermatocytes, secondary spermatocytes, and finally spermatids within the tubular lumen. Thirteen stages of germ cell differentiation have been identified in humans. The tight junctions of Sertoli cells support spermatogonia and early spermatocytes within the basal compartment while all subsequent stages of germ cell development occur within the adluminal compartment. Germ cells are staged by their histologic morphology; there are dark type A (Ad) and pale type A (Ap) and type B spermatogonia and preleptotene, leptotene, zygotene, and pachytene primary spermatocytes, secondary spermatocytes, and Sa, Sb, Sc, Sd_1, and Sd_2 spermatids (Figure 44–3).



▲ **Figure 44–3.** Testicular germ cell maturation from spermatogonium to spermatid.

Spermatogenesis is a cyclic process that involves the division of spermatogonial stem cells into elongated spermatids. Several individual cycles of spermatogenesis coexist within the germinal epithelium at a given time. In humans, an entire spermatogenic cycle requires approximately 60–80 days. Cohorts of developmentally similar germ cells are linked by cytoplasmic bridges and mature in unison. This cytoplasmic linkage of cells is organized in a spiral pattern along the seminiferous tubule and results in relatively stable rather than pulsatile production of mature sperm.

Genetics of Spermatogenesis

Mitosis is the process by which somatic cells are replicated to form genetically identical daughter cells. **Meiosis** is the process by which germ cells replicate. As the result of meiosis, daughter cells called **gametes** are formed, which contain one-half the genetic material of the parent cell and thus allow for reproduction. This fundamental difference in cell replication generates genetic diversity through natural selection.

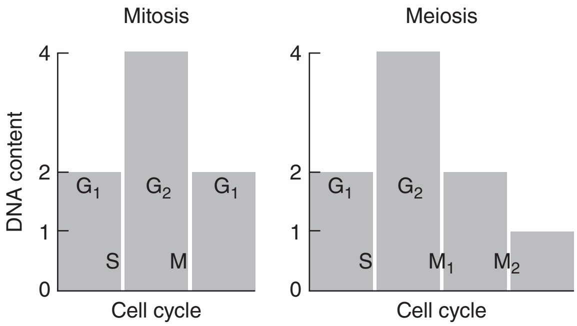
A cell's life is divided into cycles that are each associated with different DNA replication activities. Only 5–10% of the cell cycle is spent in the mitotic phase (M), during which time genetic (DNA) and cellular division occur. Mitosis is a precise series of events that requires complete duplication of the genetic material (chromosomes), degeneration of the nuclear envelope, and equal division of chromosomes and cytoplasm into two daughter cells (Table 44–2). The difference between mitotic and meiotic replication is that in mitosis, a single DNA duplication is followed by one cell division; however, in meiosis, two cell divisions take place to create four daughter cells (Figure 44–4). As a consequence, following meiosis, daughter cells (gametes) contain only half of the chromosome content of the parent cell and are said to be haploid (*n*) as opposed to diploid (2*n*). Other major differences between mitosis and meiosis are outlined in Table 44–3.

Stages of Spermatogenesis

From puberty onward, the process of spermatogenesis requires rapid and organized cell division, the likes of which are not seen in other cell lines of the human body. As a result, these highly specialized cells are produced in large quantities; up to 300 sperm per gram of testis tissue per second. Type B spermatogonia undergo mitosis to produce diploid primary spermatocytes (2*n*), which then duplicate their DNA during interphase. After the first meiotic division, each daughter cell contains a single partner of the homologous chromosome pair and are termed secondary spermatocytes (2*n*). During the second meiotic division the chromatids separate at the centromere, yielding haploid spermatids (*n*).

Table 44–2. Phases of the cell cycle and mitosis.

Mitotic phase	Cell cycle	Description of events
Interphase	G_1, S, G_2	DNA doubling occurs
Prophase	M	Nuclear envelope degenerates; spindle forms
Metaphase	M	Chromosomes align at cell equator
Anaphase	M	Duplicated chromosomes separate
Telophase	M	Chromosomes to poles, cytoplasm divides



▲ **Figure 44–4.** Changes in nuclear DNA content with mitosis and meiosis. (G = growth phase; M = mitotic phase; S = DNA synthesis phase.)

Spermiogenesis

Spermiogenesis is the process by which spermatids mature to become elongated spermatozoa within the basilar compartment of the seminiferous tubules. This process requires several weeks and includes (1) formation of the acrosome from the Golgi body, (2) formation of the flagellum from the centriole, (3) reorganization of the mitochondria around the midpiece, (4) extensive compaction of nuclear material, and (5) elimination of residual cytoplasm.

Many cellular elements contribute to the cellular morphologic changes during spermiogenesis, including chromosome structure, associated chromosomal proteins, the perinuclear cytoskeletal theca layer, the microtubules in the nucleus, subacrosomal actin, and Sertoli cell interactions. With completion of spermatid elongation, the Sertoli cell cytoplasm retracts around the developing sperm, stripping it of all unnecessary cytoplasm and extruding it into the tubule lumen. The mature sperm has remarkably little cytoplasm.

Sperm Maturation

Testicular spermatozoa have limited or no motility and are therefore incapable of naturally fertilizing an egg (which has significant clinical implications). While motile sperm can often be found within the testicle, the vast majority gain this ability only after traversing the epididymis where further maturation occurs. Anatomically, the epididymis is divided into 3 regions: caput or head, corpus or body, and cauda or tail. While the process of epididymal sperm maturation is still being elucidated, it is clear that several changes occur in sperm as they transit through the epididymis. These changes include alterations in cell membrane polarity, membrane protein composition, immunoreactivity, phospholipid and fatty-acid content, and adenylate cyclase activity. A sperm's transit time through the epididymis is approximately 10–15 days.

Table 44–3. Essential differences between mitosis and meiosis within seminiferous tubules.

Mitosis	Meiosis
1 cell division, 2 daughter cells	2 cell divisions, 4 daughter cells
Chromosome number maintained	Chromosome number halved
No pairing, chromosome homologs	Synapse of homologs, prophase I
No crossovers	>1 crossover per homolog pair
Centromeres divide, anaphase	Centromeres divide, anaphase II
Identical daughter genotype	Genetic variation in daughter cells

FERTILIZATION

During natural conception, fertilization generally occurs within the ampulla of the fallopian tubes. Ovulation typically occurs during the middle of the female menstrual cycle and can be predicted by timing, change in body temperature, chemical detection of the luteinizing hormone surge, or by changes in cervical mucus. This mucus becomes more abundant and watery, thereby facilitating the entry of sperm into the uterus and protecting it from the acidic vaginal environment. Once within the female reproductive tract, sperm undergo physiologic changes in membrane fluidity, collectively referred to as **capacitation**. These changes allow sperm to hyperactivate, a process characterized by profound changes in motility (large, lashing motions of the sperm tail). On contact with the egg, lytic enzymes are released from the acrosome to allow penetration of the outer surface of the egg. On completion of the acrosome reaction, further contact between sperm and egg is mediated by specific ligands and receptors on the surface of each gamete.

Once a single sperm enters the zona pellucida of the ovum, it becomes impenetrable to additional sperm. On fertilization, the egg resumes meiosis and forms a metaphase II spindle. The sperm centriole, contained within the midpiece is crucial for early spindle formation and ongoing embryogenesis.

DIAGNOSIS OF MALE INFERTILITY

The purpose of the male infertility evaluation is to (1) identify and correct the reversible causes of male infertility with the goal of allowing a couple to conceive through intercourse, or with the least amount of technology; (2) identify irreversible conditions that may be amenable to treatment with assisted reproductive technology (ART) using the male partner's sperm; (3) identify irreversible conditions in which the man's sperm are not obtainable, in which case the couple may consider donated sperm or adoption; (4) identify medical diseases that may be associated with infertility and require treatment; and (5) identify specific genetic causes of infertility that may be transmitted to and impact offspring. Given that a male factor can be the cause of infertility in 30–40% of couples and is a contributing factor in 50% of cases, it is important to evaluate both partners in parallel. A comprehensive urologic evaluation is important because male infertility may be the presenting symptom of otherwise occult but significant systemic disease.

HISTORY

The evaluation of male infertility begins with a thorough reproductive, medical, and surgical history (Table 44–4). Important components of this history include (1) duration of infertility, coital timing and frequency, and sexual health; (2) prior paternity or fertility treatments; (3) childhood illnesses and development; (4) medical illnesses, prior infections, and medications; (5) prior surgeries or traumas; (6) exposure to potential environmental gonadal toxins, such as heat, radiation, chemical solvents, or pesticides; and (7) exposure to potential lifestyle-based gonadal toxins, such as tobacco, marijuana, alcohol and other recreational drugs.

A sexual history is important as many couples do not know how to precisely time intercourse to achieve a pregnancy. Following intercourse, sperm reside within the cervical mucus and crypts for 1–2 days and can survive longer; thus an appropriate frequency of intercourse is every 2 days. Water-based lubricants such as K-Y jelly, most skin lotions, and saliva can reduce sperm motility in vitro and should be avoided. If needed, acceptable lubricants include vegetable, safflower, coconut, and peanut oils as well as egg whites.

A general medical and surgical history is also important. Fever or acute infection can decrease testis function and semen quality. Given that spermatogenesis generally requires at least 60 days to complete, the impact of such insults may not be observable in the semen until at least 2 months after the event. Surgical procedures on the bladder, retroperitoneum, or pelvis can lead to infertility by causing ejaculatory dysfunction due to damage to the bladder neck, sympathetic nerves or pelvic nerve plexus, respectively. Hernia surgery is a rare cause of obstruction of the vas deferens.

Childhood diseases can have a significant impact on fertility. Severe unilateral orchitis occurs in approximately one third of postpubertal mumps infections and bilateral orchitis in 10%. Mumps orchitis likely causes pressure necrosis of testis tissue due to severe edema with later development of testis atrophy. Mumps is uncommon among children from countries with mandatory vaccination plans. Cryptorchidism is associated with decreased sperm production. This is true for both unilateral and bilateral cases. Longitudinal studies of affected boys have shown that abnormally low sperm counts can be found in 30% of men with unilateral cryptorchidism and 50% of men with bilateral undescended testes. While difficult to study from an epidemiologic standpoint, cryptorchidism appears to result in a higher risk of infertility. Similar to

Table 44–4. Components of infertility history.

Fertility history
- Previous pregnancies (all partners)
- Duration of infertility
- Previous infertility treatments
- Female evaluation

Sexual history
- Libido
- Erections
- Timing and frequency
- Lubricants

Developmental history
- Cryptorchidism
- Childhood cancer/treatment
- Mumps orchitis
- Pubertal development

Medical history
- Fevers
- Systemic illness—diabetes, cancer, infection
- Genetic diseases—cystic fibrosis, Klinefelter syndrome

Surgical history
- Orchidopexy, cryptorchidism
- Herniorrhaphy
- Trauma, torsion
- Pelvic, bladder, or retroperitoneal surgery
- Transurethral resection for benign prostatic hyperplasia
- Pubertal onset

Family history
- Cryptorchidism
- Midline defects (Kartagener syndrome)
- Hypospadias
- Exposure to diethylstilbestrol
- Other rare syndromes (prune belly, etc)

Medications
- Testosterone
- DHEA
- Finasteride/dutasteride
- Opioids
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Nitrofurantoin
- Cimetidine
- Sulfasalazine
- Spironolactone
- α-Blockers

Social history
- Ethanol
- Smoking/tobacco
- Marijuana
- Cocaine
- Anabolic steroids

Occupational history
- Exposure to ionizing radiation
- Chronic heat exposure (saunas)
- Aniline dyes
- Pesticides
- Heavy metals (lead)

Table 44–5. Medications associated with impaired ejaculation.

- Antihypertensive agents (thiazides)
- α-Adrenergic blockers (prazosin, phentolamine)
- Antipsychotic agents
  - Mellaril (thioridazine)
  - Haldol (haloperidol)
  - Librium
- Antidepressants
  - Imipramine
  - Amitriptyline

testicular cancer risk, early orchidopexy may reduce the risk of spermatogenic failure.

Exposure and medication histories are very relevant to fertility. Both prescription and over-the-counter medications can severely impact semen quality. Decreased sperm counts have been demonstrated in workers exposed to specific pesticides, which may alter normal testosterone/estrogen hormonal balance. Exposure to ionizing radiation can cause temporary reductions in sperm production with as little as 10 cGy and more permanent or severe reductions with higher doses. Several medications (Table 44–5) and ingestants such as tobacco, cocaine, and marijuana have all been implicated as gonadotoxins. With the legalization of marijuana in several states, heavy exposure may become more common and likely more impactful. The effects of these agents may be reversible on withdrawal, although few studies have been performed. Anabolic steroids, often taken to increase muscle mass and development, act as contraceptives by inhibiting the pituitary–gonadal axis. Routine exposure to moist heat by use of hot tubs or saunas should be discouraged, as these activities can elevate intratesticular temperature and impair sperm production. Other characteristics associated with impaired fertility include obesity, electromagnetic radiation exposure (eg, significant exposure to high-voltage power lines, cellphones in the "on" position), occupational status (eg, dry cleaners, painters, farm workers), and job-related or other psychological stress.

The family and developmental histories may also provide clues to the infertility etiology. A family history of cystic fibrosis (CF), a condition associated with congenital absence of the vas deferens (CAVD), or intersex conditions is important. The existence of siblings with fertility problems may suggest that a Y chromosome microdeletion or a cytogenetic (karyotype) abnormality is present in the family. A history of delayed onset of puberty could suggest Kallmann or Klinefelter syndrome. A history of recurrent respiratory tract infections may suggest a ciliary defect characteristic of the immotile cilia syndromes (eg, Kartagener syndrome). It is important to remember that reproductive technologies enable most men afflicted with such conditions to father children and therefore allow for the perpetuation of genetic abnormalities that may not be normally sustained.

PHYSICAL EXAMINATION

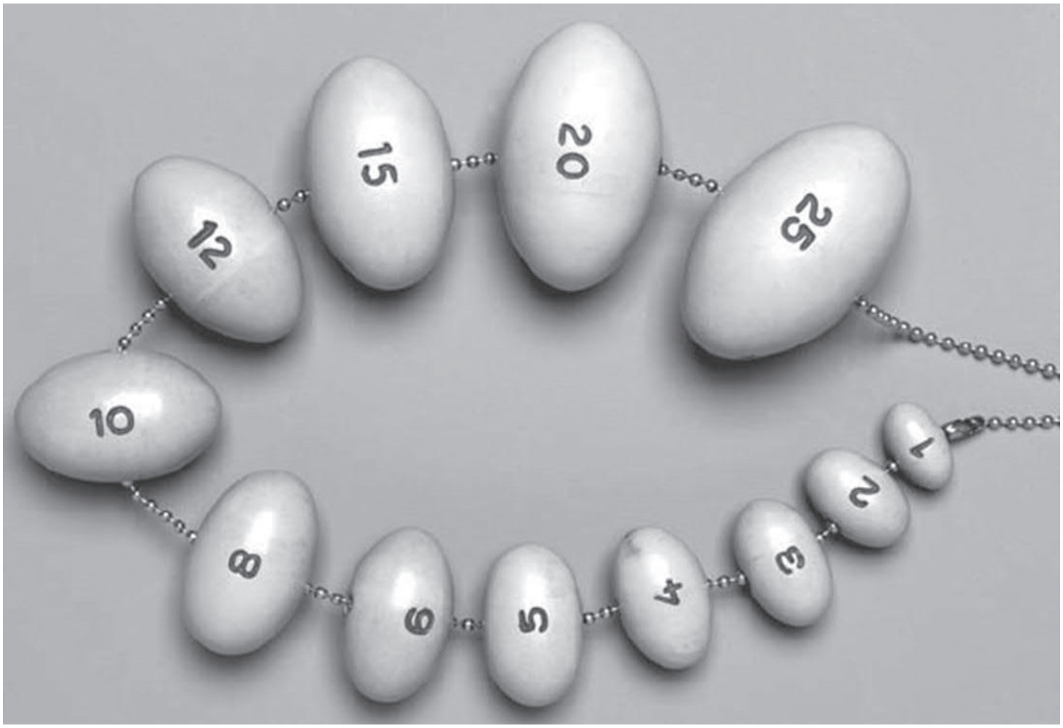
A complete examination of the infertile male is important to identify general health issues associated with infertility. The patient should be virilized as signs of decreased body hair or gynecomastia may suggest androgen deficiency or estrogen excess.

The scrotal contents should be carefully palpated with the patient standing. It is psychologically uncomfortable for young men to have the testes examined, and therefore it is helpful to make the examination as efficient and matter-of-fact as possible. Three features should be noted about the testis: size, consistency, and any associated abnormalities. Size is assessed by measuring the long axis and width; as an alternative, an orchidometer can be placed next to the testis for volume determination (Figure 44–5). Standard values of testis size have been reported for normal men and include a mean testis length of 4.6 cm (range 3.6–5.5 cm), a mean width of 2.6 cm (range 2.1–3.2 cm), and a mean volume of 18.6 mL (± 4.6 mL) (Figure 44–6). Consistency is more difficult to assess but can be described as firm (normal) or soft (abnormal). Testes that are smaller than normal volume are termed **hypotrophic**, whereas those that are softer than normal are termed **atrophic**. Both conditions suggest impaired spermatogenesis. The presence of testicular mass or lesion would inform additional evaluations to rule out testicular germ cell cancer.

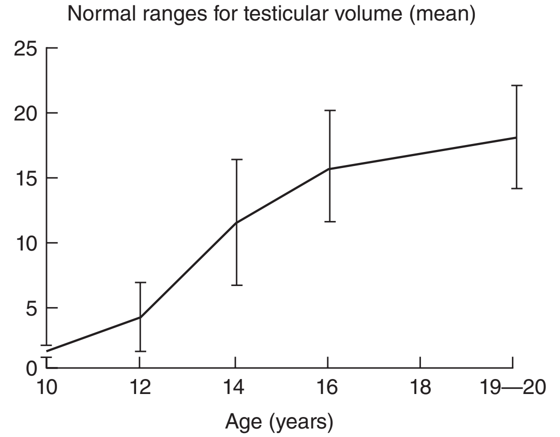
The peritesticular area should also be examined. Irregularities of the epididymis, located posterior-lateral to the testis, include induration, tenderness, or cysts. The presence or absence of the scrotal vas deferens is critical to observe, as 2% of infertile men may present with CAVD.

Engorgement of the pampiniform plexus of veins in the scrotum is indicative of a varicocele. Asymmetry of the spermatic cords is the usual initial observation, followed by the feeling of a "bag of worms" when retrograde blood flow through the pampiniform veins occurs with a Valsalva maneuver. Varicoceles are usually found on the left side (90%) and may be associated with atrophy of the testis. A discrepancy in testis size between the right and left sides should alert the clinician to this possibility.

Prostate or penile abnormalities should also be noted. Penile abnormalities such as hypospadias, abnormal curvature, or phimosis could result in inadequate delivery of semen to the upper vaginal vault during intercourse. Prostatic infection may be detected by the finding of a boggy, tender prostate on rectal examination. Prostate cancer, often suspected with unusual firmness or a nodule within the prostate, can occasionally be diagnosed in infertile men. Loss of prostate contour in a man with low ejaculate volume may indicate a persistent prostate utricle. Enlarged seminal vesicles, indicative of ejaculatory duct obstruction, may also be palpable on rectal examination.



▲ **Figure 44–5.** **Prader orchidometer for measuring testicular volume.** (Reproduced with permission from McClure RD: Endocrine investigation and therapy, Urol Clin North Am. 1987 Aug;14(3):471–488.)



▲ **Figure 44–6.** **Normal values for testicular volume in relation to age.** (Data from Zachman M et al: Testicular volume during adolescence: Cross-sectional and longitudinal studies, Helv Paediatr Acta. 1974 Apr; 29(1):61–72; McClure RD: Endocrine investigation and therapy, Urol Clin North Am. 1987 Aug;14(3):471–488.)

LABORATORY TESTING

Laboratory testing is an important part of the male infertility evaluation.

Semen Analysis

A carefully performed semen analysis is the primary source of information on sperm production and reproductive tract patency. However, it is not a measure of functional fertility. An abnormal semen analysis simply suggests the likelihood of decreased fertility. Studies have established that there are certain limits of adequacy below which it may be difficult to initiate a pregnancy. These semen analysis values were identified by the World Health Organization (2010) and are considered the minimum criteria for "normal" semen quality (Table 44–6; see also Table 44–7). It is statistically more difficult to achieve a pregnancy if a semen parameter falls below any of those listed. Of these semen variables, the count and motility appear to correlate best with fertility.

A. Semen Collection

Semen quality can vary widely in a normal individual from day to day, and semen analysis results are dependent

Table 44–6. Semen analysis[a]—minimal standards of adequacy.

Ejaculate volume	≥1.5 mL
Sperm concentration	>15 × 10^6 sperm/mL
Motility	>40%
Morphology	≥4% normal forms

[a] No agglutination (clumping), white cells, or increased viscosity.

Data from Cooper TG, Noonan E, von Eckardstein S, et al: World Health Organization reference values for human semen characteristics, Hum Reprod Update. 2010 May-Jun;16(3):231–245.

on collection technique. For example, the period of sexual abstinence before sample collection is a large source of variability. With each day of abstinence (up to 1 week), semen volume can rise by up to 0.4 mL, and sperm concentration can increase by 10–15 million/mL. Sperm motility tends to fall when the abstinence period is longer than 5 days. For this reason, it is recommended that semen be collected after 48–72 hours of sexual abstinence.

To establish a baseline of semen quality, at least two semen samples are needed. Semen should be collected by self-stimulation, by coitus interruptus (less ideal), or with a special, nonspermicidal condom into a clean glass or plastic container. Because sperm motility decreases after ejaculation, the specimen should be analyzed within 1 hour of procurement. During transit, the specimen should be kept at body temperature.

B. Physical Characteristics and Measured Variables

Fresh semen is a coagulum that liquefies 15–30 minutes after ejaculation. Ejaculate volume should be at least 1.5 mL, as smaller volumes may not sufficiently buffer against vaginal acidity. Low ejaculate volume may indicate retrograde ejaculation, ejaculatory duct obstruction, incomplete collection, or androgen deficiency. Sperm concentration should be >15 million sperm/mL. Sperm motility is assessed in two ways: (1) the fraction of sperm that are moving and (2) the quality of sperm movement (how fast, how straight they swim).

Sperm cytology or morphology is another measure of semen quality. By assessment of the exact dimensions and shape characteristics of the sperm head, midpiece, and tail, sperm can be classified as “normal” or not. In the strictest classification system (Kruger morphology), at least 5% of sperm in the ejaculate must be normal in appearance for semen morphology to be considered “normal.”

Table 44–7. Frequency of semen analysis findings in infertile men.

Findings	Percent
All normal	55
Isolated abnormal	37
Low motility	26
Low count	8
Volume	2
Morphology	1
No sperm	8

C. Computer-Assisted Semen Analysis

In an effort to remove the subjective variables inherent in the manually performed semen analysis, computer-aided semen analyses (CASA) couple video technology with digitalization and microchip processing to categorize sperm features by algorithms. Although the technology is promising, when manual semen analyses are compared to CASA on identical specimens, CASA can overestimate sperm counts by 30% with high levels of contaminating cells such as immature sperm or leukocytes. In addition, at high sperm concentrations, motility can be underestimated with CASA. CASA has accepted value in the research setting and in some clinical laboratories.

D. Semen Leukocyte Analysis

White blood cells (leukocytes) are present in all ejaculates and play important roles in immune surveillance and clearance of abnormal sperm. Leukocytospermia or pyospermia, an increase in leukocytes in the ejaculate, is defined as >1 × 10^6 leukocytes/mL semen but is not a significant cause of male subfertility, and its treatment is debated. The prevalence of leukocytospermia ranges from 2.8% to 23% of infertile men. In general, neutrophils predominate among inflammatory cells (Table 44–8). This condition is detected by a variety of diagnostic assays, including differential stains (eg, Papanicolaou), peroxidase stain that detects the peroxidase enzyme in neutrophils, and immunocytology. These tests are important to confirm elevated leukocyte levels rather than seminal “round cells” that represent immature germ cells.

Table 44–8. Cells involved in leukocytospermia.

Cell type	Relative abundance
Neutrophils	++++
Monocyte/macrophage	+
T-helper lymphocytes	+
T-suppressor lymphocytes	++
B lymphocytes	+

Antisperm antibodies (ASAs) can be found in three locations: serum, seminal plasma, and sperm-bound. Among these, sperm-bound antibodies are the most relevant. The antibody classes that appear to be clinically relevant include immunoglobulin G (IgG) and IgA. IgG antibody is derived from local production and from transudation from the bloodstream (1%). IgA is believed to be purely locally derived.

Adjunctive Semen Tests: Seminal Fructose and Post-ejaculate Urinalysis

Fructose is a carbohydrate that is secreted in high concentration from the seminal vesicles and is normally present in the ejaculate. When absent, seminal vesicle agenesis or obstruction may exist. Seminal fructose testing is indicated in men with low ejaculate volumes and no sperm. A postejaculate urinalysis inspects the first voided urine after ejaculation for the presence of sperm. If sperm is identified in the urine, a diagnosis of retrograde ejaculation is made. This test is indicated when the ejaculate volume is below normal (Table 44–7).

Antisperm Antibody Test

The testis is an immunologically privileged site owing to the blood–testis barrier. Autoimmune infertility may result when the blood–testis barrier is broken and the body is exposed to sperm antigens. Trauma to the testis and vasectomy may lead to antigen exposure, giving rise to antisperm antibodies (ASA). ASA may be associated with impaired sperm transport through the reproductive tract or impairment in egg fertilization. An assay for ASA should be considered when (1) semen analyses show persistent sperm agglutination or clumping, (2) there is low sperm motility with history of testis injury or surgery, (3) there is idiopathic leukocytospermia, or (4) there is unexplained infertility. In the modern era of fertility treatment, ASA are rarely tested, as their presence is not treated directly.

Hypoosmotic Swelling Test

Motility is the most commonly used measure of a sperm's viability. Studies have suggested however, that some nonmotile sperm may still be viable. Indeed, there are clinical conditions, such as immotile cilia syndrome or testicular sperm, in which there may be immotile but otherwise healthy, viable sperm. Given that these sperm may be used in conjunction with intracytoplasmic sperm injection to form healthy embryos, it is clinically important that they be identifiable. Cell viability can be evaluated noninvasively by using the physiologic principle of hypoosmotic swelling. Viable cells with functional membranes swell when placed in a hypoosmotic environment. This response is easily observed in sperm as tail coiling generally accompanied by head swelling. This sperm test is indicated in cases of complete absence of sperm motility.

Sperm Penetration Assay

It is possible to measure the ability of human sperm to penetrate a specially prepared hamster egg in the laboratory setting. The hamster egg allows interspecies fertilization but no further development. This form of bioassay can give important information about the ability of sperm to undergo the capacitation process as well as penetrate and fertilize the egg. Infertile sperm would be expected to penetrate and fertilize a lower fraction of eggs than normal sperm. The indications for the diagnostic sperm penetration assay (SPA) are limited to situations in which functional information about sperm are needed, that is, to further evaluate couples with unexplained infertility and to help couples decide whether intrauterine insemination (IUI) (good SPA result) or IVF and micromanipulation (poor SPA result) is the appropriate next treatment. This test is rarely ordered or used today.

Sperm DNA Fragmentation Assay

The integrity of sperm DNA is important for male fertility. Double- and single-stranded breaks in sperm DNA can be measured by several methods, including the COMET and TUNNEL assays with or without the use of flow cytometry. These tests assess the degree of DNA fragmentation that occurs after chemically stressing the sperm DNA-chromatin complex, and can indirectly reflect the quality of sperm DNA-chromatin complex, and can indirectly reflect the quality of sperm DNA integrity. Abnormally fragmented sperm DNA rarely occurs in fertile men, but can be found in a larger percentage of infertile men with otherwise normal semen analyses. This test can detect infertility that is missed on a conventional semen analysis. Often reversible, causes of DNA fragmentation include tobacco use, medical disease, hyperthermia, air pollution, infections, and varicocele. Sperm DNA fragmentation testing should only be performed in select men in who testing may inform treatment choices.

Hormone Assessment

Evaluation of the pituitary–gonadal axis provides valuable information on the state of sperm production. Further, abnormal function of the HPG axis can be an underlying cause of poor sperm production and infertility (hyperprolactinemia, gonadotropin deficiency, congenital adrenal hyperplasia). In general, FSH and testosterone should be measured in infertile men with sperm concentrations of $<10 \times 10^6$ sperm/mL. Testosterone is a measure of overall endocrine balance and likely plays a critical role in spermatogenesis. In most cases, FSH reflects the state of sperm production; when spermatogenesis is impaired at the testicular level, FSH should be elevated. This combination of tests will detect most (99%) endocrine abnormalities. Serum LH and prolactin levels may be obtained if testosterone and FSH are abnormal. In the setting of low testosterone, free testosterone should be assessed. Given the role of estradiol in regulating the HPG axis, it, too,

Table 44–9. Characteristic endocrine profiles in infertile men.

Condition	T	FSH	LH	PRL
Normal	NL	NL	NL	NL
Primary testis failure	Low	High	NL/high	NL
Hypogonadotropic hypogonadism	Low	Low	Low	NL
Hyperprolactinemia	Low	Low/NL	Low	High
Androgen resistance	High	High	High	NL

FSH = follicle-stimulating hormone; LH = luteinizing hormone; NL = normal; PRL = prolactin; T = testosterone.

should be assessed if there is evidence of poor virilization or obesity. Thyroid hormone, liver function, and other organ-specific tests should be obtained if there is clinical evidence of active disease, as uncontrolled systemic illness can affect sperm production. The common patterns of hormonal disorders observed in infertility are given in Table 44–9.

With relatively normal spermatogenesis, low levels of plasma LH and FSH have no clinical meaning; likewise, an isolated low LH with normal testosterone is not significant. Additional indications for hormone evaluation of infertile men include impaired sexual function (low libido, erectile dysfunction) and findings suggestive of a specific endocrinopathy (eg, thyroid). On initial testing, approximately 10% of infertile men will have an abnormal hormone level, with clinically significant endocrinopathies occurring in 2% of men.

GENETIC TESTING

Chromosomal Studies

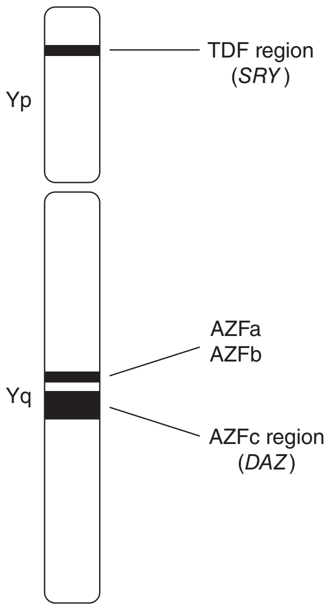
Subtle genetic abnormalities can present as male infertility. It is estimated that between 2% and 15% of infertile men with azoospermia (no sperm count) or severe oligospermia (low sperm counts) will harbor a chromosomal abnormality on either the sex chromosomes or the autosomes. A blood test for cytogenetic analysis (karyotype) can determine if such a genetic anomaly is present. Patients at risk for abnormal cytogenetic findings include men with small, atrophic testes, elevated FSH values, and azoospermia. Klinefelter syndrome (XXY) is the most frequently detected sex chromosomal abnormality among infertile men.

Cystic Fibrosis Mutation Testing

A blood test is indicated for infertile men who present with CF or the much more subtle condition, CAVD. Similar genetic mutations are found in both patients, although the latter group is generally considered to have an atypical form of CF, in which the scrotal vas deferens is nonpalpable. Approximately 80% of men without palpable vasa will harbor a CF gene mutation. Recent data also indicate that azoospermic men with idiopathic obstruction and men with a clinical triad of chronic sinusitis, bronchiectasis, and obstructive azoospermia (Young syndrome) may be at higher risk for CF gene mutations.

Y-Chromosome Microdeletion Analysis

As many as 7% of men with oligospermia and 15% of azoospermic men have small, underlying deletions in one or more gene regions on the long arm of the Y chromosome (Yq). Several regions of the Y chromosome have been implicated in spermatogenic failure, identified as *AZF a*, *b*, and *c* (Figure 44–7). Deletion of the *DAZ* (deleted in azoospermia) gene in the *AZFc* region is the most commonly observed microdeletion in infertile men. Fertility is possible in most men with these deletions with IVF and micromanipulation of sperm. A polymerase chain reaction-based blood test can examine the Y chromosome from peripheral leukocytes for these gene deletions and is recommended for men with low or no sperm counts and small, atrophic testes.



▲ **Figure 44–7.** Regions of the Y chromosome that have been associated with male infertility include azoospermia factor (AZF) regions *a*, *b*, and *c*. The *AZFc* region contains the *DAZ* gene, one of the few true infertility genes isolated to date. (TDF = testis-determining factor.)

ADJUNCTIVE TESTS

Urinalysis

A urinalysis is a simple test that can be performed during the initial office visit. It may indicate the presence of infection, hematuria, glucosuria, or renal disease, and as such may suggest anatomic or medical problems within the urinary tract.

Semen Culture

Seminal fluid that passes through the urethra is routinely contaminated with bacteria. This can make the interpretation of semen culture difficult. Semen cultures should be obtained only in selected situations, and approximately 13% of infertile men will have positive semen cultures; the relationship between bacterial cultures and infertility is controversial. Semen cultures should be considered when there is evidence of infection, including (1) a history of genital tract infection, (2) abnormal expressed prostatic secretion, (3) the presence of more than 1000 pathogenic bacteria per milliliter of semen, and (4) the presence of $>1 \times 10^6$ leukocytes/mL of semen (pyospermia).

The agents most commonly responsible for male genital tract infections are listed in Table 44–10. Gonorrhea is the most common infection. About 10–25% of chlamydial infections may be asymptomatic. *Trichomonas vaginalis* is a protozoan parasite responsible for 1–5% of nongonococcal infections; it is usually symptomatic. *Ureaplasma urealyticum* is a common inhabitant of the urethra in sexually active men (30–50% of normal men) and is responsible for one-fourth of all cases of nongonococcal infections. *Escherichia coli* infections are relatively uncommon in young men and are usually symptomatic. **Mycoplasmas** are aerobic bacteria that are known to colonize the male reproductive tract. Rarer but possible causes of infection include anaerobic bacteria and tuberculosis.

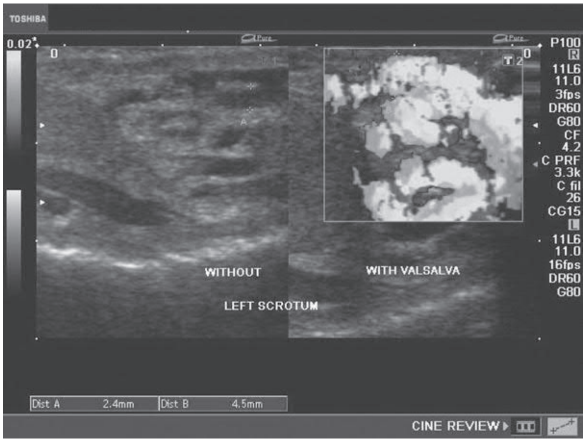
Radiologic Testing

A. Scrotal Ultrasound

High-frequency ultrasound of the scrotum is commonly performed for the evaluation of testicular, paratesticular, and scrotal lesions that cannot be completely evaluated on physical examination. Scrotal ultrasound is indicated in men who have a hydrocele that renders the testis nonpalpable. Any abnormality of the peritesticular region should also undergo a scrotal ultrasound to determine its characteristics or origin.

Table 44–10. Most common organisms in male genital infection.

Neisseria gonorrhoeae	Cytomegalovirus
Chlamydia trachomatis	Herpes simplex II
Trichomonas vaginalis	Human papilloma virus
Ureaplasma urealyticum	Epstein–Barr virus
Escherichia coli (other Gram-negative bacilli)	Hepatitis B virus
Mycoplasma hominis	Human immunodeficiency virus



▲ **Figure 44–8.** Scrotal ultrasound. Varicoceles are imaged as tubular echo-free structures. (Reproduced with permission from McClure RD, Hricak H: Scrotal ultrasound in the infertile male. Detection of subclinical unilateral and bilateral varicoceles, J Urol. 1986 Apr;135(4):711–715.)

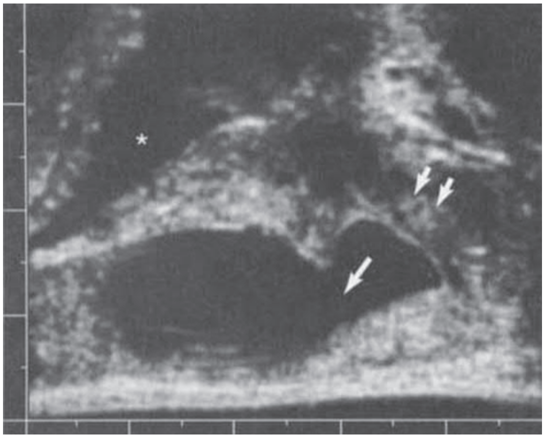
Scrotal color Doppler ultrasonography has been used to investigate varicoceles (Figure 44–8). By combining measurements of blood flow patterns (the presence of retrograde venous flow) and vein size, both physiologic and anatomic information can be obtained to confirm the diagnosis. Although diagnostic criteria that define a varicocele vary widely, a pampiniform venous diameter of >3 mm is considered abnormal. Retrograde blood flow through the veins with a Valsalva maneuver is a key radiologic feature of a varicocele.

B. Transrectal Ultrasound

High-frequency (5–7-mHz) transrectal ultrasound (TRUS) can provide good anatomic detail of the prostate, seminal vesicles, and ejaculatory ducts. Dilation of the seminal vesicles (>1.5 cm in width) or ejaculatory ducts (>2.3 mm), in association with a cyst, calcification, or stones along the duct is highly suggestive of obstruction (Figure 44–9). Among infertile men, TRUS is indicated in cases of low ejaculate volume (<1.5 mL) not explained by retrograde ejaculation or abnormal hormones.

C. Computed Tomography Scan or Magnetic Resonance Imaging of the Pelvis

The imaging techniques of computed tomography (CT) and magnetic resonance imaging (MRI) can further define reproductive tract anatomy. However, since the advent of TRUS, these studies have relatively few indications. They include evaluation of a patient with a solitary right varicocele, which

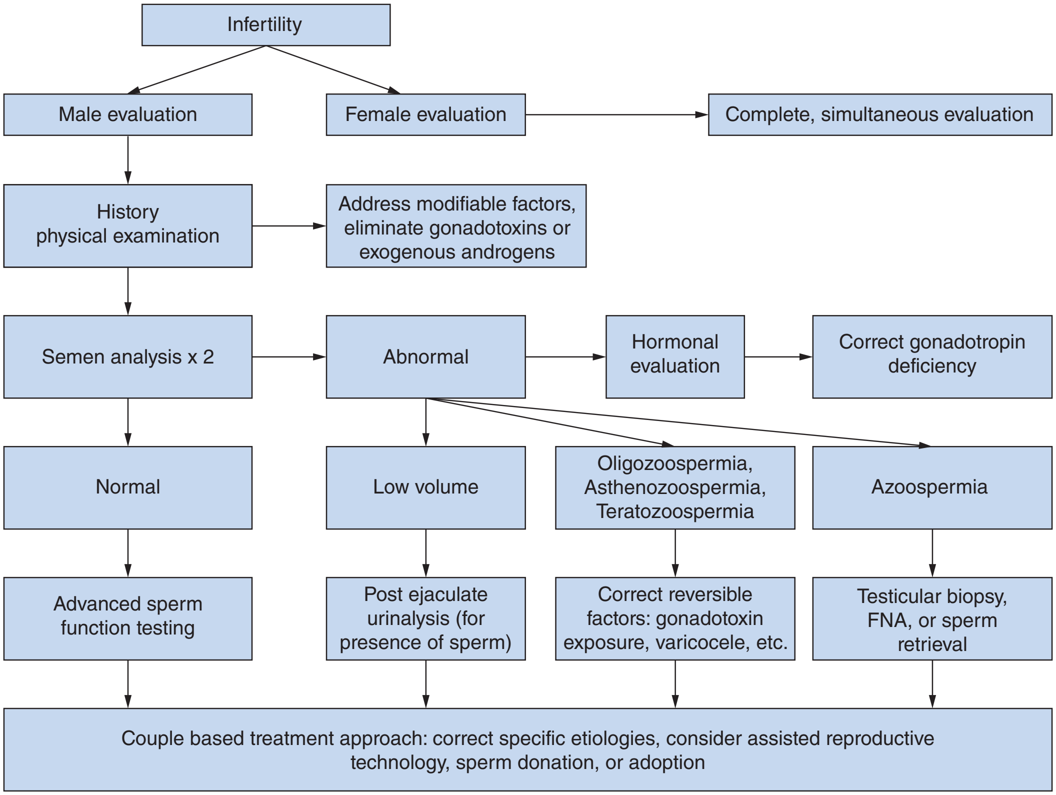


▲ Figure 44–9. Transrectal ultrasonography (sagittal view) in a man with low ejaculate volume and low sperm counts and motility. Ejaculatory duct cyst (*white arrow*); urethra (*double white arrows*); bladder (*asterisk*).

may be associated with retroperitoneal pathology, and evaluation of the nonpalpable testis.

Testis Biopsy and Vasography

The diagnostic testis biopsy is an important adjunct to the infertility evaluation as it provides direct information regarding the state of spermatogenesis. Most commonly, the technique involves a small, open incision in the scrotal wall and testis tunica albuginea under local or general anesthesia. A small sample of testis tissue is removed, fixed in formalin or Bouin's solution, and examined histologically. Abnormalities of seminiferous tubule architecture and cellular composition are then categorized into several patterns. This procedure is generally reserved for azoospermic men, in whom it may be difficult to distinguish between a failure of sperm production (nonobstructive azoospermia (NOA) and obstruction within the reproductive tract ducts (obstructive azoospermia [OA]). A testis biopsy allows delineation between these conditions and can guide further treatment options in azoospermic men (Figure 44–10).


Infertility
Male evaluation
Female evaluation
Complete, simultaneous evaluation
History physical examination
Address modifiable factors, eliminate gonadotoxins or exogenous androgens
Semen analysis x 2
Abnormal
Hormonal evaluation
Correct gonadotropin deficiency
Normal
Low volume
Oligozoospermia, Asthenozoospermia, Teratozoospermia
Azoospermia
Advanced sperm function testing
Post ejaculate urinalysis (for presence of sperm)
Correct reversible factors: gonadotoxin exposure, varicocele, etc.
Testicular biopsy, FNA, or sperm retrieval
Couple based treatment approach: correct specific etiologies, consider assisted reproductive technology, sperm donation, or adoption

▲ Figure 44–10. Algorithm for evaluation of azoospermia or no sperm in the ejaculate. (ACTH = adrenocorticotrophic hormone; CBAVD = congenital bilateral absence of the vas deferens; CF = cystic fibrosis; FNA = fine-needle aspiration; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.) (Data from Turek PJ: Practical approaches to the diagnosis and management of male infertility, Nat Clin Pract Urol. 2005 May;2(5):226–238.)

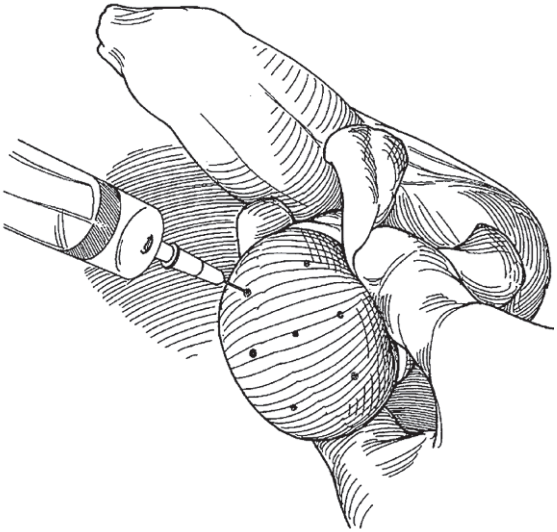
In azoospermic men with normal ejaculate volume and evidence of normal spermatogenesis by testis biopsy, formal investigation of the reproductive tract to identify the site of obstruction is warranted. A vasogram involves the injection of contrast media into the vas deferens toward the bladder from the scrotum. In plain-film radiographs or fluoroscopy, contrast material can delineate the proximal vas deferens, seminal vesicle, and ejaculatory duct anatomy and determine whether obstruction is present. Similar information, albeit without anatomic detail, can be obtained with chromotubation, whereby dye (indigo carmine, methylene blue) is injected while the ejaculatory ducts are visualized by cystourethroscopy. Sampling of vasal fluid during the same procedure can also determine whether sperm exist within the testicular end of the vas deferens. Vasal sperm presence implies that there is no obstruction in the testis or epididymis. With this information, the site of obstruction can be accurately determined and potentially surgically corrected.

Biopsy is rarely indicated for oligospermia unless it is severe or alternates with azoospermia (cryptozoospermia), or a patient who is clinically diagnosed with NOA. While a unilateral testis biopsy is usually sufficient, the finding of asymmetric testes warrants bilateral biopsies. This situation may reflect a unilateral unobstructed failing testis paired with a normal obstructed testis. Historically, testis biopsy has been proposed to identify patients at high risk for intratubular germ cell neoplasia. This premalignant condition exists in 5% of men with a contralateral germ cell tumor of the testis and is more prevalent in infertile than fertile men. Significantly, while there is strong evidence that infertile men have higher risk for testicular cancer, their absolute risk for cancer remains low and most cancers will present with a painless testicular mass. In general, the purpose of biopsy is for the purpose of identifying the presence or absence of sperm, and not for cancer diagnosis.

Testis sperm extraction (TESE) may be performed to obtain sperm for use with assisted reproductive technology. Testicular sperm that are harvested surgically are now routinely used to help men with severe male-factor infertility to achieve fatherhood. Sperm retrieval techniques are discussed in subsequent sections.

Multisite Fine-Needle Aspiration of Testes (Figure 44–11)

Testicular sperm is used with IVF and ICSI to achieve pregnancies; however, there is a failure to obtain sperm in 25–50% of men with spermatogenic failure. When testis sperm retrieval procedures fail to retrieve sperm, IVF cycles are canceled at great emotional and financial cost. To minimize the chance of failed sperm retrieval, percutaneous fine-needle aspiration of the testis has been described. This technique can accurately diagnose and classify the severity of disease in men with azoospermia or severe oligospermia. Cytological analysis with FNA has a high correlation with histological specimens from open testicular biopsies. In some men, FNA may be more sensitive at detecting a heterogenous pattern of intratesticular spermatogenesis.



▲ **Figure 44–11.** Technique of percutaneous fine-needle aspiration "mapping" for sperm in the testis. Cytologic samples are taken from various systematically sampled areas of the testis, guided by marks on the scrotum. (Reproduced with permission from Turek PJ, Cha I, Ljung BM: Systematic fine-needle aspiration of the testis: correlation to biopsy and results of organ "mapping" for mature sperm in azoospermic men, Urology. 1997 May;49(5):743–748.)

Similar to a testis biopsy, fine-needle aspiration is performed under local anesthesia. Percutaneously aspirated (with a 23-gauge needle) seminiferous tubules from various locations in the testis are smeared on a slide, fixed, stained, and read by an experienced andrologist or cytopathologist for the presence of sperm. The information gained from this technique can fully inform patients of their chances of subsequent sperm retrieval for IVF and ICSI. However, for many patients, diagnostic information gained from these biopsies do not change their subsequent decision to proceed with micro-TESE (microsurgical testicular sperm extraction), the technique necessary to extract sperm for men with NOA. Many men will proceed with micro-TESE even with unfavorable diagnostic test results.

CAUSES OF MALE INFERTILITY

The causes underlying male infertility are numerous and best categorized by effects at one or more of the following levels: pretesticular, testicular, and posttesticular.

Table 44–11. Pretesticular causes of infertility.

Hypothalamic disease
Gonadotropin deficiency (Kallmann syndrome)
Isolated LH deficiency ("fertile eunuch")
Isolated FSH deficiency
Congenital hypogonadotropic syndromes
Pituitary disease
Pituitary insufficiency (tumors, infiltrative processes, operation, radiation, deposits)
Hyperprolactinemia
Exogenous hormones (estrogen–androgen excess, glucocorticoid excess, hyper- and hypothyroidism)
Growth hormone deficiency

PRETESTICULAR

Conditions that cause infertility that act at the pretesticular level tend to be hormonal in nature (Table 44–11).

Hypothalamic Disease

A. Gonadotropin Deficiency (Kallmann Syndrome)

Kallmann syndrome (1:30,000) is characterized by central hypogonadism, delayed in puberty, and infertility. Other clinical features include anosmia, small testes and occasionally renal agenesis, bimanual synkinesia, cleft lip, and dental agenesis. When anosmia is not present, the condition is termed **idiopathic hypogonadotropic hypogonadism (IHH)**. The clinical diagnosis of Kallmann syndrome is confirmed by hormonal assessment revealing low testosterone, low LH, low FSH, and normal prolactin levels. Infertility is treatable with gonadotropin (LH and FSH) replacement over 12–18 months, which induces sperm in the ejaculate in 80% of men. The condition is inherited as a familial disorder in one-third of cases, and both X-linked and autosomal inheritance patterns have been described. In the X-linked recessive form, deletions of the *KAL1* gene prevent migration of GnRH neurons to the preoptic area of the hypothalamus during embryologic development.

Virilization and fertility can be achieved when FSH and LH are given to stimulate testis function.

B. Isolated Gonadotropin Deficiencies

These deficiencies are rare. As the result of a partial LH deficit, there is enough LH to stimulate intratesticular testosterone production and spermatogenesis but insufficient testosterone to promote virilization. The result is a eunuchoid body habitus, variable virilization, and gynecomastia. These men usually have normal-size testes, but sperm concentration is low. Plasma FSH levels are normal, but serum LH and testosterone levels are low-normal.

With insufficient FSH production by the pituitary patients are normally virilized, testicular size is normal, and LH and testosterone levels are normal. FSH levels are uniformly low and do not respond to stimulation with GnRH. Sperm counts range from azoospermia to severely low numbers (oligospermia).

C. Congenital Hypogonadotropic Syndromes

Several syndromes may be associated with secondary hypogonadism. Prader–Willi syndrome (1:20,000) is characterized by obesity, mental retardation, small extremities, and hypogonadism and is caused by a deficiency of hypothalamic GnRH. The cause of this condition appears to be a single gene deletion on chromosome 15. Similar to Kallmann syndrome, spermatogenesis can be induced by treatment with FSH and LH. Bardet–Biedl syndrome is an autosomal recessive form of hypogonadotropic hypogonadism that also results from GnRH deficiency. It is characterized by mental retardation, retinitis pigmentosa, polydactyly, and hypogonadism. The presentation is similar to Kallmann syndrome but includes obesity and may also be treated with gonadotropin administration. Cerebellar ataxia can be associated with hypogonadotropic hypogonadism. Cerebellar involvement includes abnormalities of speech and gait, and these patients can have a eunuchoid appearance with atrophic testes. Hypothalamic–pituitary dysfunction due to pathologic changes in cerebral white matter is thought to underlie infertility.

Pituitary Disease

A. Pituitary Insufficiency

Pituitary insufficiency may result from tumors, infarcts, surgery, radiation, or infiltrative and granulomatous processes. In sickle cell anemia, pituitary and testicular microinfarcts result from sickling of red blood cells potentially leading to both hypogonadism and spermatogenic failure. Men with sickle cell anemia have decreased testosterone and variable LH and FSH levels. β-Thalassemia occurs primarily in patients of Mediterranean or African origin and is caused by mutations in the β-globulin that leads to abnormal hemoglobin composition and subsequent red cell lysis. Infertility results from the deposition of hemosiderin in the pituitary gland and testes. Similarly, hemochromatosis results in iron deposition within the liver, testis, and pituitary and is associated with testicular dysfunction in 80% of cases.

B. Hyperprolactinemia

Elevations of circulating prolactin can cause hypogonadotropic hypogonadism. If hyperprolactinemia is identified, secondary causes such as stress during a blood draw, systemic illness, or medications should be ruled out. With these causes excluded, the most common and important cause of hyperprolactinemia is a prolactin-secreting pituitary adenoma, or prolactinoma. Magnetic resonance imaging (MRI) of the sella turcica has classically been used to distinguish between microadenoma (<10 mm) and macroadenoma (>10 mm) forms of tumor.

Stratification of disease based on radiologic diagnosis alone is misleading, as surgery for hyperprolactinemia almost always reveals a pituitary tumor. Elevated prolactin typically results in suppression of gonadotropin production, with subsequent declines in testosterone levels and spermatogenesis. Symptoms of hyperprolactinemia may include loss of libido, erectile dysfunction, gynecomastia, and galactorrhea. Signs and symptoms of other pituitary hormone derangements (adrenocorticotropic hormone, thyroid-stimulating hormone) should also be investigated.

C. Exogenous or Endogenous Hormones

1. Estrogens—An excess of sex steroids, either estrogens or androgens, may cause infertility due to an imbalance of the testosterone:estrogen ratio, which is normally 10:1. Liver cirrhosis increases endogenous estrogens as a result of augmented aromatase activity within the diseased liver. Likewise, obesity may be associated with testosterone and estrogen imbalance owing to increased peripheral aromatase activity in adipocytes. Less commonly, adrenocortical tumors, Sertoli cell tumors, and interstitial testis tumors may produce estrogens. Excess estrogens cause spermatogenic failure by decreasing pituitary gonadotropin secretion thus inducing secondary testis failure.

2. Androgens—An excess of androgens can suppress pituitary gonadotropin secretion and lead to secondary testis failure. The use of exogenous androgenic steroids (anabolic steroids) by as many as 15% of high school athletes, 30% of college athletes, and 70% of professional athletes (in selected sports) may result in temporary sterility due to suppression of the normal HPG axis. Treatment includes immediate discontinuation of steroids and reevaluation of semen quality every 3–6 months until spermatogenesis returns. The most common reason for excess endogenous androgens is congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. The resultant absence of cortisol synthesis and excessive adrenocorticotropic hormone production leads to elevated androgenic steroids by the adrenal cortex. High androgen levels in prepubertal boys results in precocious puberty, with premature development of secondary sex characteristics and abnormal enlargement of the phallus. The testes are characteristically small because of central gonadotropin inhibition by androgens. In young girls, virilization occurs with clitoral enlargement. In cases of classic congenital adrenal hyperplasia that presents in childhood, normal sperm counts and fertility have been reported, even without glucocorticoid treatment. This disorder is one of the few intersex conditions associated with potentially normal fertility. Other sources of endogenous androgens include hormonally active adrenocortical tumors or Leydig cell tumors of the testis.

3. Hyper- and hypothyroidism—Thyroid abnormalities are a rare cause (0.5%) of male infertility. Abnormally high or low levels of serum thyroid hormone impact spermatogenesis at the level of both the pituitary and testis. Euthyroidism is important for normal hypothalamic hormone secretion and for normal sex hormone-binding protein levels that govern the testosterone:estrogen ratio.

TESTICULAR

Many conditions that cause infertility act at the testicular level (Table 44–12). Unlike many pretesticular conditions, which are treatable with hormonal manipulation, testicular defects are mostly irreversible.

Common Genetic Causes

A. Y-Chromosome Microdeletions

Approximately 7% of men with low sperm counts and 13% with azoospermia have a structural alteration in the long arm of the Y chromosome (Yq). The testis-determining region genes that control testis differentiation are intact, but there may be gross deletions in other regions that may lead to defective spermatogenesis. The recent explosion in molecular genetics has allowed for sophisticated analysis of the Y chromosome. At present, three gene sites are being investigated as putative AZF (azoospermia factor) candidates: *AZF a, b,* and *c*. The most promising site is *AZFc,* which contains the *DAZ* gene region. The gene, of which there are at least six copies in this region, appears to encode a ribonucleic acid (RNA)-binding protein that regulate the meiotic pathway during germ cell production. Homologs of the *DAZ* gene are found in many other animals, including mouse and *Drosophila.* A quantitative polymerase chain reaction (PCR)-based assay is used to test blood for these deletions. In the future, sperm DNA may also be tested as part of a semen analysis. Since men with these microdeletions can have sperm in the ejaculate, they are likely to pass them on to offspring if assisted reproductive technology is used.

Table 44–12. Testicular causes of infertility.

Chromosomal (Klinefelter syndrome [XXY], XX sex reversal, XYY syndrome)
Noonan syndrome (male Turner syndrome)
Myotonic dystrophy
Vanishing testis syndrome (bilateral anorchia)
Sertoli-cell-only syndrome (germ cell aplasia)
Y-chromosome microdeletions (*DAZ*)
Gonadotoxins (radiation, drugs)
Systemic disease (renal failure, liver failure, sickle cell anemia)
Defective androgen activity
Testis injury (orchitis, torsion, trauma)
Cryptorchidism
Varicocele
Idiopathic

B. Klinefelter Syndrome

Abnormalities in chromosomal number (aneuploidy) are well-recognized causes of male infertility. In a study of 1263 infertile couples, a 6.2% overall prevalence of chromosomal abnormalities was detected. Among men whose sperm count was <10 million/mL, the prevalence was 11%. In azoospermic men, 21% had significant chromosomal abnormalities. For this reason, cytogenetic analysis (karyotype) of autosomal and sex chromosomal anomalies should be considered in men with severe oligospermia and azoospermia.

Klinefelter syndrome is the most common chromosomal aneuploidy and a common genetic cause of azoospermia, accounting for up to 14% of cases in some series (overall incidence 1:500 males). The classic triad of findings is: small, firm testes; gynecomastia; and azoospermia. Some men may present with delayed sexual maturation, increased height, decreased intelligence, varicosities, obesity, diabetes, leukemia, increased likelihood of extragonadal germ cell tumors, and breast cancer (20-fold higher than in normal males). Among men with Klinefelter's, 90% have an extra X chromosome (47, XXY) and 10% are mosaic, with a combination of XXY/XY chromosomes. The testes are usually <2 cm in length and always <3.5 cm; biopsies show sclerosis and hyalinization of the seminiferous tubules with normal numbers of Leydig cells. Hormones usually demonstrate decreased testosterone and frankly elevated LH and FSH levels. Serum estradiol levels may also be elevated. With age, testosterone levels decline, and most men will require androgen replacement therapy both for virilization and for normal sexual function. Paternity with this syndrome is rare but more likely in the mosaic or milder form of the disease. Some men will have limited spermatogenesis whereby sperm may be retrieved from the testicles and used with ICSI to cause pregnancy.

Other Genetic Causes and Syndromes

A. XX Male Syndrome

The XX male syndrome is a structural and numerical chromosomal condition, a variant of the Klinefelter syndrome that presents as gynecomastia at puberty or as azoospermia in adults. Average height is below normal, and hypospadias is common. Male external and internal genitalia are otherwise normal. The prevalence of mental deficiency is not increased. Hormone evaluation shows elevated FSH and LH and low or normal testosterone levels. Testis biopsy reveals absent spermatogenesis with fibrosis and Leydig cell clumping. The most obvious explanation is that sex determining ratio (SRY), or the testis-determining region, is translocated from the Y to the X chromosome. Thus, testis differentiation is present; however, the genes that control spermatogenesis on the Y chromosome are not similarly translocated, resulting in azoospermia.

B. XYY Syndrome

The prevalence of XYY syndrome is similar to that of Klinefelter, but the clinical presentation is more variable. Typically, men with 47,XYY are tall, and 2% exhibit aggressive or antisocial behavior. Hormone evaluation reveals elevated FSH and normal testosterone and LH levels. Semen analyses show either oligospermia or azoospermia. Testis biopsies vary but usually demonstrate arrest of maturation or Sertoli-cell-only syndrome.

C. Noonan Syndrome

Also called **male Turner syndrome**, Noonan syndrome is associated with clinical features similar to those of the Turner syndrome (43,X). However, the karyotype is either normal (46,XY) or mosaic (X/XY). Typically, patients have dysmorphic features like webbed neck, short stature, low-set ears, wide-set eyes, and cardiovascular abnormalities. At birth, 75% have cryptorchidism that limits fertility in adulthood. If testes are fully descended, then fertility is possible and likely. Associated FSH and LH levels depend on the degree of testicular function.

D. Myotonic Dystrophy

Myotonic dystrophy is the most common reason for adult-onset muscular dystrophy. In addition to having myotonia, or delayed relaxation after muscle contraction, patients usually present with cataracts, muscle atrophy, and various endocrinopathies. Most men have testis atrophy, but fertility has been reported. Infertile men may have elevated FSH and LH with low or normal testosterone, and testis biopsies show seminiferous tubule damage in 75% of cases. Pubertal development is normal; testis damage seems to occur later in life.

E. Vanishing Testis Syndrome

Also called bilateral anorchia, vanishing testis syndrome is rare, occurring in 1:20,000 males. Patients present with bilateral nonpalpable testes and sexual immaturity due to the lack of testicular androgens. The testes are lost due to fetal torsion, trauma, vascular injury, or infection. In general, functioning testis tissue must have been present during weeks 14–16 of fetal life, since Wolffian duct growth and Müllerian duct inhibition occur along with appropriate growth of male external genitalia. Patients have eunuchoid body proportions but no gynecomastia. The karyotype is normal. Serum LH and FSH levels are elevated, and serum testosterone levels are extremely low. There is no treatment for this form of infertility; patients receive lifelong testosterone for normal virilization and sexual function.

F. Complete Germ Cell Aplasia (Sertoli-Cell-Only Syndrome)

Germ cell aplasia is characterized by the complete absence of germinal cells on histologic examination of testes biopsies from an azoospermic man. Several causes have been proposed, including genetic defects, congenital absence of normal germ cell migration during embryogenesis, androgen resistance, and autoimmune cellular regression. Clinically, men are normally virilized with smaller than normal testes with normal consistency. Endocrine function of the testes are preserved and, testosterone and LH levels are normal; however, FSH levels are usually (90%) elevated. The use of the word **syndrome** implies that no recognized insult has occurred, since gonadotoxins such as ionizing radiation, chemotherapy, and mumps orchitis can also render the testes aplastic of germ cells. There is no known treatment for this condition. In some patients, extensive testis sampling with fine-needle aspiration mapping or multiple biopsies can reveal sperm that can be used for pregnancy with assisted reproductive technologies.

G. Defective DNA Mismatch Repair

Defective DNA repair has been suspected to play an etiologic role in certain cancers. Data from mice suggests that mutations in genes needed for DNA repair (PMS2, Mlh1) also leads to infertility characterized by meiotic arrest with a pattern of maturation arrest seen in testis pathology. Male infertility characterized by azoospermia and both germ cell maturation arrest and Sertoli-cell-only syndrome has also been described in association with abnormalities in DNA mismatch repair. This provides evidence that certain forms of male infertility could involve the inability to properly repair germline DNA. The relationship between defective DNA repair in infertile men and their risk of cancer as well as the risk of cancer among their biological offspring certainly merits further research.

Gonadotoxins

A. Radiation

The effects of radiotherapy on sperm production have been well described Clifton and Bremner (1983) examined the effects of ionizing irradiation on semen quality and spermatogenesis among a population of healthy prisoners in the 1960s. Before a vasectomy, each of the volunteers was exposed to various levels of radiation and found a distinct dose-dependent, inverse relationship between irradiation and sperm count. Sperm count was significantly reduced at 15 cGy, and azoospermia was temporarily induced at 50 cGy. Persistent azoospermia was induced at 400 cGy, without evidence of recovery for a minimum of 40 weeks. In most subjects, sperm counts rebounded to preirradiation levels with cessation of exposure.

Histologic examination of testis tissue after irradiation has shown that spermatogonia are most sensitive to irradiation while Leydig cell mass is relatively preserved. Given the sensitivity of germ cells to irradiation, some studies have focused on the testicular radiation exposure that occurs during radiation therapy for cancer. During abdominal radiation with gonadal shielding, the estimated mean unintended gonadal exposure is approximately 75 cGy. There does not appear to be an increase in congenital birth defects in offspring of irradiated men. Importantly, recent data has suggested that environmental or occupational exposure to electromagnetic radiation may also reduce semen quality.

Table 44–13. Medications associated with infertility.

Calcium channel blockers	Allopurinol
Cimetidine	α-Blockers
Sulfasalazine	Nitrofurantoin
Valproic acid	Lithium
Spironolactone	Tricyclic antidepressants
Colchicine	Antipsychotics
SSRIs	
Testosterone	

B. Drugs

A list of gonadotoxic medications can be found in Table 44–13. These can result in infertility by various mechanisms. Ketoconazole, spironolactone, and alcohol inhibit testosterone synthesis, whereas cimetidine is an androgen antagonist. Recreational drugs such as marijuana, heroin, and methadone are associated with lower testosterone levels. Certain pesticides, like dibromochloropropane, are likely to have estrogen-like activity. Importantly, the gonadotoxic potential of many pharmaceutical and over the counter medications is unknown. Therefore, couples should consider discontinuing and unnecessary medication or supplements prior to their attempt to conceive.

Chemotherapies intended for their cytotoxic effects on rapidly dividing cancer cells also have a profound impact on germ cells that are normally dividing at a rapid rate. Spermatogonia are the germ cells most sensitive to cytotoxic chemotherapy. Alkylating agents such as cyclophosphamide, chlorambucil, and nitrogen mustard are the most toxic agents. The effects of chemotherapeutic drugs vary according to dose and duration of treatment, type and stage of disease, age and health of the patient, and baseline testis function. Despite this toxicity, the mutagenic effects of chemotherapy agents do not appear to be significant enough to increase the chance of birth defects or genetic diseases among offspring of treated men. Patients should wait at least 6 months after chemotherapy ends before attempting to conceive.

Systemic Disease

A. Renal Failure

Uremia is associated with infertility, decreased libido, erectile dysfunction, and gynecomastia. The cause of hypogonadism is controversial and probably multifactorial. Testosterone levels are decreased, and FSH and LH levels can be elevated. Serum prolactin levels are elevated in 25% of patients. Hyperestrogenemia may play a role in hormone axis derangements and impaired spermatogenesis. Medications and uremic neuropathy may cause uremic-related impotence and a decline in libido. Renal transplantation can result in improvement in hypogonadism.

B. Liver Cirrhosis

Hypogonadism related to liver failure may have various contributing factors. The reason for organ failure is important. Hepatitis is associated with viremia, and associated fevers can affect spermatogenesis. Excessive alcohol intake inhibits testicular testosterone synthesis, independent of its liver effects. Liver failure and cirrhosis are associated with testicular atrophy, impotence, and gynecomastia. Levels of testosterone and its metabolic clearance are decreased; estrogen levels are increased owing to augmented conversion of androgens to estrogens by aromatase. Decreased testosterone levels are not accompanied by proportionate elevations in LH and FSH levels, suggesting that a central inhibition of the HPG axis may accompany liver failure.

C. Sickle Cell Disease

Sickle cell disease can cause pituitary dysfunction, likely due to the sludging of erythrocytes and associated microinfarcts. This same mechanism may also occur in testis tissue and contribute to primary hypogonadism. As a result, spermatogenesis is decreased, accompanied by lower serum testosterone levels.

D. Diabetes Mellitus

Prolonged diabetes can result in significant cardiovascular disease, as well as peripheral neuropathy. The impact of such disease on erectile and ejaculatory function has been well described. In addition to poor sexual function, neuropathy involving the parasympathetic and sympathetic pelvic plexus can lead to poor contractility of the bladder neck and ejaculatory organs resulting in retrograde or anejaculation.

▶ Defective Androgen Activity

Peripheral resistance to androgens occurs with two basic defects: (1) a deficiency of androgen production through the absence of 5α-reductase or (2) a deficiency in the androgen receptor. In general, these conditions are a consequence of single gene deletions.

A. 5α-Reductase Deficiency

5α-Reductase deficiency results in normal development of the testes and Wolffian duct structures (internal genitalia) but ambiguous external genitalia. The ambiguity results from an inborn deficiency of the 5α-reductase enzyme that converts testosterone to DHT in androgen-sensitive tissues like the prostate, seminal vesicle, and external genitalia. Thus far, 29 mutations have been described in the culprit enzyme. The diagnosis is made by measuring the ratio of testosterone metabolites in urine and confirmed by finding decreased 5α-reductase in genital skin fibroblasts. Spermatogenesis has been described in descended testes; however, fertility has not been reported in these patients. The lack of fertility may be due largely to functional abnormalities of the external genitalia.

B. Androgen Receptor Deficiency

Androgen receptor deficiency is an X-linked genetic condition marked by resistance to androgens. The androgen receptor, a nuclear protein, is absent or functionally altered such that testosterone or DHT cannot bind to it and activate target cell genes. Since androgens have no effect on tissues, both internal and external genitalia are affected. Fertility effects depend on the specific receptor abnormality. Some patients are 46,XY males with complete end-organ resistance to androgens. They have female external genitalia with intra-abdominal testes. Testes show immature tubules and the risk of testis cancer is elevated; tumors will develop in 10–30% of patients without orchiectomy. Fertility is absent. Patients with mild receptor defects may present as normal-appearing infertile men. Spermatogenesis may be present, although impaired. It is unclear exactly how common this occurs in infertile men.

▶ Testis Injury

A. Orchitis

Inflammation of testis tissue is most commonly due to bacterial infection, termed **epididymoorchitis**. Viral infections also occur in the testis in the form of mumps orchitis. Orchitis is observed in approximately 30% of postpubertal males who develop mumps parotitis. Testis atrophy is a significant and frequent result of viral orchitis but is less common with bacterial infections.

B. Torsion

Ischemic injury to the testis secondary to twisting of the testis on the spermatic cord pedicle is common in prepubertal and early postpubertal boys. When diagnosed and corrected surgically within 6 hours of occurrence, the testis can usually be saved. Torsion may result in inoculation of the immune system with testis antigens that may predispose the subject to later immunological infertility. It recognized that the “normal” contralateral mate of a torsed testis could also exhibit histologic abnormalities. It has not been clearly demonstrated whether this is related to the actual torsion or to an underlying abnormality in testes predisposed to torsion.

C. Trauma

Trauma to the testis can result in infertility. Because of the unique immunologic status of the testis in the body (ie, it is an immunologically privileged site), trauma to the testis can invoke an abnormal immune response in addition to atrophy resulting from injury. Both may contribute to infertility.

Trauma to the testis that results in fracture of the testis tunica albuginea should be surgically explored and repaired to minimize exposure of testis tissue to the body.

Cryptorchidism

Cryptorchidism or undescended testis is a common urologic problem, observed in 0.8% of boys at 1 year of age. Failure of the testis to descend places it at higher risk of developing testicular germ cell cancer. Although the newborn undescended testis may be morphologically normal, deterioration in germ cell numbers is often seen by 2 years of age. The contralateral, normally descended testis is also at increased risk of harboring germ cell abnormalities. Thus, males with either unilaterally or bilaterally undescended testes are at risk for spermatogenic failure and infertility later in life. Historically, orchidopexy was performed solely for the purpose of testicle palpation to allow for cancer detection. However, we now understand that when performed prior to puberty, orchidopexy reduces the risk of cancer development. Further, early orchidopexy can improve spermatogenesis in cryptorchid boys.

Varicocele

Varicocele is the result of retrograde venous blood flow through incompetent veins of the pampiniform plexus of spermatic cord. Varicocele has been described as the most common surgically correctable cause of male subfertility. This disease develops during puberty when both endocrine and exocrine function of the testicle dramatically increases, along with testicular blood flow. Varicocele is only rarely detected in boys <10 years of age. A left-sided varicocele is found in 15% of healthy young men. In contrast, the incidence of a left varicocele in subfertile men approaches 40%. Bilateral varicoceles are uncommon in healthy men (<10%) but are palpated in up to 20% of subfertile men. Varicoceles do not spontaneously regress. An accurate physical examination is the cornerstone of varicocele diagnosis; however, ultrasound can be a powerful tool for detection is uncertainty remains after physical examination.

Several anatomic features contribute to the predominance of left-sided varicoceles. The left internal spermatic vein is longer than the right, and it typically joins the left renal vein at a right angle compared to the oblique insertion of the right spermatic vein into the inferior vena cava. As a result of these characteristics, higher venous pressures are transmitted to the left spermatic cord veins and result in retrograde reflux of blood.

Varicoceles are associated with testicular atrophy, and their correction can reverse atrophy in adolescents. There is strong evidence that varicocele affects semen quality, causing abnormalities in concentration, motility, and morphology; however, deficits in motility can be the most profound. The finding of semen abnormalities constitutes the most common indication for varicocele surgery in infertile men.

The mechanism by which varicocele exerts an effect on the testicle remains unclear. Several theories have been postulated and it is likely that a combination of effects results in infertility. Pituitary-gonadal hormonal dysfunction, internal spermatic vein reflux of renal or adrenal metabolites, and an increase in hydrostatic pressure associated with venous reflux are also postulated effects of a varicocele. The most intriguing theory of how varicoceles affect testis function invokes an inhibition of spermatogenesis through the reflux of warm corporeal blood around the testis, with disruption of the normal countercurrent heat exchange balance and elevation of intratesticular temperature.

Idiopathic

It has been estimated that nearly half of male infertility has no readily identifiable cause. The etiology of male infertility is likely multifactorial, encompassing genetic, endocrine, and environmental factors. Additionally, modifiable lifestyle characteristics may make a significant contribution to the disease. The effects of physical activity, obesity, alcohol, tobacco and marijuana use, psychological stress, and cellphone usage on male infertility have been examined in a few observational studies, yet results are inconclusive due to limitations in study design.

POSTTESTICULAR (TABLE 44–14)

Reproductive Tract Obstruction

The posttesticular portion of the reproductive tract includes the epididymis, vas deferens, seminal vesicles, and associated ejaculatory apparatus.

Table 44–14. Posttesticular causes of infertility.

Reproductive tract obstruction
Congenital blockages
Congenital absence of the vas deferens (CAVD)
Young syndrome
Idiopathic epididymal obstruction
Polycystic kidney disease
Ejaculatory duct obstruction
Acquired blockages
Vasectomy
Groin surgery
Infection
Functional blockages
Sympathetic nerve injury
Pharmacologic
Disorders of sperm function or motility
Immotile cilia syndromes
Maturation defects
Immunologic infertility
Infection
Disorders of coitus
Erectile dysfunction
Hypospadias
Timing and frequency

A. Congenital Blockages

1. Cystic fibrosis—CF is the most common autosomal recessive genetic disorder in the United States with a carrier frequency of 1:20 among Caucasians. The disease is caused by defective chloride ion transport across cell membranes resulting in fluid and electrolyte abnormalities (abnormal chloride–sweat test). CF typically presents with chronic lung obstruction and pulmonary infections, pancreatic insufficiency, and infertility. Greater than 95% of men with CF also have congenital bilateral absence of the vas deferens (CBAVD). In addition to the vas, parts of the epididymis, seminal vesicles, and ejaculatory ducts may be atrophic or absent, causing obstruction. Although spermatogenesis is quantitatively normal, recent data suggest that sperm from men with CF may lack the normal capacity to fertilize an egg. Further, some carriers of abnormal CF genes may also have functional sperm defects. CBAVD accounts for 1–2% of infertility cases. On physical examination, no palpable vas deferens is observed on one or both sides. As in CF, the rest of the reproductive tract ducts may also be abnormal and reconstruction is not feasible. This disease is related to CF. Even though most of these men demonstrate no symptoms of CF, up to 80% of patients will harbor a detectable CF mutation. Among men with unilateratal absence of the vas deferens, 15% will have absence of the ipsilateral kidney due to embryologic induction anomalies.

2. Young syndrome—Young syndrome presents with a triad of chronic sinusitis, bronchiectasis, and obstructive azoospermia. The obstruction is in the epididymis. The pathophysiology of the condition is unclear but may involve abnormal ciliary function or abnormal mucus quality. Reconstructive surgery is associated with lower success rates than that observed with other obstructed conditions.

3. Idiopathic epididymal obstruction—Idiopathic epididymal obstruction is a relatively uncommon condition found in otherwise healthy men. There is recent evidence linking this condition to CF in that one-third of men so obstructed may harbor CF gene mutations.

4. Adult polycystic kidney disease—Adult polycystic kidney disease is an autosomal dominant disorder associated with numerous cysts of the kidney, liver, spleen, pancreas, epididymis, seminal vesicle, and testis. Disease onset usually occurs in the twenties or thirties with symptoms of abdominal pain, hypertension, and renal failure. Infertility with this disease is usually secondary to obstructing cysts in the epididymis or seminal vesicle.

5. Blockage of the ejaculatory ducts—Blockage of the ejaculatory ducts, the delicate, paired, collagenous tubes that connect the vas deferens and seminal vesicles to the urethra, is termed ejaculatory duct obstruction. It is the cause of infertility in 5% of azoospermic men. Obstruction can be congenital and result from Müllerian duct (utricular) cysts, Wolffian duct (diverticular) cysts, or congenital atresia or is acquired from seminal vesicle calculi or postsurgical or inflammatory scar tissue. It presents as hematospermia, painful ejaculation, or infertility. The diagnosis is confirmed by finding a low-volume ejaculate and TRUS showing dilated seminal vesicles or dilated ejaculatory ducts.

B. Acquired Blockages

1. Vasectomy—Vasectomy is performed on more than 0.5 million men per year in the United States for contraception. Subsequently, 6% of these men have the vasectomy reversed, most commonly because of remarriage.

2. Groin and hernia surgery—Groin and hernia surgery can result in inguinal vas deferens obstruction in 1% of cases. There has been concern that synthetic mesh products used for hernia repairs may add to perivasal inflammation and increase the likelihood of vassal obstruction.

3. Bacterial infections—Bacterial infections (*E. coli* in men age >35 years) or *Chlamydia trachomatis* in young men) may involve the epididymis, with scarring and obstruction.

C. Functional Blockages

Besides physical obstruction, functional obstruction of the seminal vesicles may exist. Functional blockages may result from nerve injury or medications that impair the contractility of seminal vesicle or vasal musculature. A classic example of nerve injury affecting ejaculation is after retroperitoneal lymph node dissection for testis cancer. This can cause either retrograde ejaculation or complete anejaculation, depending on the degree of injury to postganglionic sympathetic fibers arising from the thoracolumbar spinal cord. These autonomic nerves overlie the inferior aorta and coalesce as the hypogastric plexus within the pelvis and control seminal emission. Multiple sclerosis and diabetes are other conditions that result in disordered ejaculation.

Evidence from animal models indicates that the seminal vesicles possess contractile properties similar to those of the urinary bladder, suggesting that seminal vesicle organ dysfunction may underlie some cases of ejaculatory duct "obstruction." Medications implicated in this functional problem are those classically associated with ejaculatory impairment. Table 44–5 (above, earlier in this chapter) lists these medications.

▶ Disorders of Sperm Function or Motility

A. Immotile Cilia Syndromes

Immotile cilia syndromes are a heterogeneous group of disorders (1:20,000 males) in which sperm motility is reduced or absent. The sperm defects are due to abnormalities in the motor apparatus or axoneme of sperm and other ciliated cells. Normally, nine pairs of microtubules are organized around a central microtubule pair within the sperm tail and are connected by dynein arms (ATPase) that regulate microtubule and therefore sperm tail motion. Various defects in the dynein arms cause deficits in ciliary and sperm activity. Kartagener syndrome is a subset of this disorder (1:40,000 males) that presents with the triad of chronic sinusitis, bronchiectasis, and situs inversus. Most immotile cilia cases are diagnosed in childhood with respiratory and sinus difficulties. Cilia present in the retina and ear may also be defective and lead to retinitis pigmentosa and deafness in Usher's syndrome. Men with immotile cilia characteristically have nonmotile but viable sperm in normal numbers. The diagnosis can only be confirmed with electron microscopy of sperm.

B. Immunologic Infertility

Autoimmune infertility has been implicated as a cause of infertility in 10% of infertile couples. The testis is an immunologically privileged site, probably owing to the blood–testis barrier, which consists of Sertoli cell tight junctions and locally downregulated cellular immunity. Autoimmune infertility may result from an abnormal exposure to sperm antigens as the result of vasectomy, testis torsion, or biopsy, which then incites a pathologic immune response. Antibodies may disturb sperm transport or disrupt sperm–egg interaction. Many assays are available to detect ASAs, but assays that detect sperm-bound, and not serum, antibodies are the most clinically relevant.

C. Infection

The agents most commonly responsible for male genital tract infections are listed in Table 44–10. Various products of activated leukocytes can exist in infected semen. A correlation exists between leukocytes in semen and the generation of superoxide anions, hydrogen peroxide, and hydroxyl radicals (reactive-oxygen species), all of which can damage sperm membranes. Sperm are highly susceptible to the effects of oxidative stress because they possess little cytoplasm and therefore little antioxidant activity. Damage to sperm from oxidative stress has been correlated with loss of function and damaged DNA. Although genital tract infection has been linked to infertility in epidemiologic studies, the correlation between individual organisms and infertility is unclear. Uncontrolled studies suggest that pregnancy rates may improve after treatment, but controlled studies do not confirm these findings.

▶ Disorders of Coitus

A. Erectile Dysfunction

Sexual dysfunction stemming from low libido or erectile dysfunction is a frequent cause of infertility. The male hormonal evaluation can detect organic reasons for such problems. Most cases of situational erectile dysfunction, in which the stress of attempting to conceive results in poor erections, are treated with sexual counseling and oral phosphodiesterase inhibitors.

B. Hypospadias

Anatomic problems such as hypospadias can cause inappropriate placement of the seminal coagulum too distant from the cervix and result in infertility.

C. Timing and Frequency

Simple problems of coital timing and frequency can be corrected by a review of the couple's sexual habits. An appropriate frequency of intercourse is every 2 days, performed within the periovulatory period, the window of time surrounding ovulation when egg fertilization is possible. Charting of basal body temperature by the female partner allows for the calculation of that period for the next ovulatory cycle. Home kits that detect the LH surge in the urine before ovulation are also helpful. Couples should be counseled to avoid lubricants if at all possible. It is also wise to discontinue any unnecessary medications during attempts to conceive. Other coital toxins include heat exposure from regular saunas, hot saunas, hot tubs, or Jacuzzis and the use of cigarettes, cocaine, marijuana, and excessive alcohol.

TREATMENT OF MALE INFERTILITY

SURGICAL TREATMENT

The role of surgery in the treatment of certain causes of male infertility is well established and cost-effective when compared to high-technology approaches. Surgeries that attempt to reverse specific anatomic or pathophysiologic defects may result in normalization or improvement in semen quality, thus allowing a couple to conceive naturally rather that will the use of assisted reproductive technology (ART). Other surgeries are for the purpose of obtaining sperm directly from the testis or epididymis and are intended to be used in conjunction with ART.

▶ Varicocele

The association of varicoceles with male infertility is well established. Several treatment modalities, both surgical and nonsurgical, are available for varicoceles. These include ligation of the veins through the retroperitoneal, inguinal, or subinguinal approaches; percutaneous embolization; and laparoscopy. The common goal of all treatments is to stop the retrograde flow of venous blood through the internal spermatic veins. Treatments can be compared in terms of expected success rates (semen improvement and pregnancy), cost, and outcomes (pain pills, return to work or other activity), and their relative merits can be analyzed. A basic comparison of three treatment options is outlined in Table 44–15. Remember that if watchful waiting is chosen, a pregnancy

Table 44–15. Varicocele treatments: comparison of outcomes.

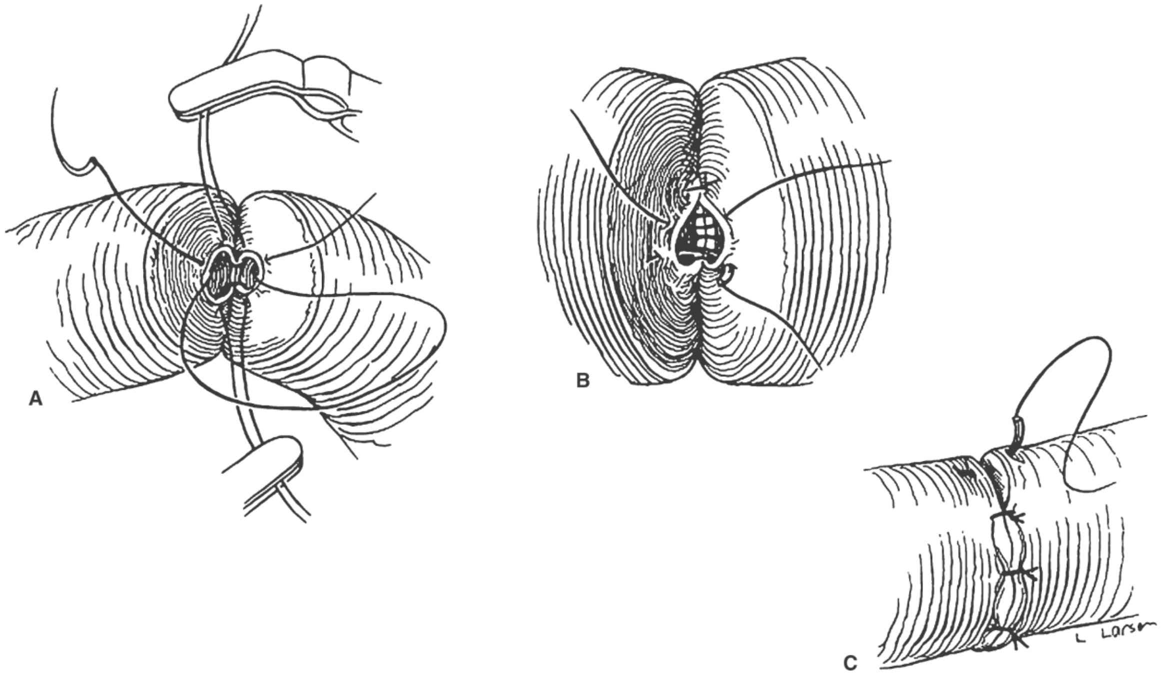
Outcome Parameter	Treatment		
	Incisional	**Laparoscopic**	**Radiologic**
Semen improvement	66%	50–70%	60%
Pregnancy rate	35%	12–32%	10–50%
Recurrence	0–15%	5–25%	0–10%
Technical failure	Negligible	Small	10–15%
Pain pills	9.4	11	Minimal
Days to work	5.0	5.3	1

rate of 16% can be expected. If IVF is chosen, a pregnancy rate of 35% can be expected. An overall complication rate of 1% is associated with the incisional approach, compared with a 4% complication rate for laparoscopy and 10–15% for radiologic occlusion. A significant problem with the radiologic approach is technical failure, meaning the inability to access and occlude the spermatic vein.

Vasectomy Reversal

More than 500,000 men per year undergo vasectomy in the United States, and nearly 6% will eventually wish to have their vasectomies reversed. The most common reasons relate to changes in a man's social circumstances and include remarriage and the loss of a child. Causes of vasal obstruction other than vasectomy include infection, congenital, trauma, and previous surgery and are less frequent indications for vasovasostomy or epididymovasostomy. A problem with duct obstruction should be suspected in men with normal testis size, normal hormones and azoospermia.

Several methods have been described for vasovasostomy. None has proved superior to any other, except that magnification with a surgical microscope results in higher success rates. Generally, either a single-layer anastomosis or a two-layer anastomosis is performed (Figure 44–12). Although these procedures are technically different, the experience of the surgeon is the most important factor for success. Depending on these factors, 95% or more of patients may have a return



▲ **Figure 44–12.** Two-layer microsurgical vasovasostomy. ***A:*** Mucosal stitches of 10–0 nylon are placed in the "back wall" of the vas lumen, incorporating mucosa and a small amount of submucosal tissue. ***B:*** The "front wall" mucosal sutures are then placed. ***C:*** Finally, serosal sutures of 9–0 nylon are placed in the outside wall of the vas deferens to complete the anastomosis. (Reproduced with permission from McClure RD: Microsurgery of the male reproductive system, World J Urol. 1986;Sep;4(2):105–114.)

of sperm after a vasovasostomy. If vasal fluid below the level of the vasectomy does not contain sperm, there may be a secondary obstruction in the epididymis. Such obstruction may result from rupture of the epididymal tubules in response to increased luminal pressure. A prolonged period of vasectomy or a vasectomy close to the epididymis increases the risk of an epididymal blockage. In this case, the vas must be connected to the epididymis above the area of rupture (i.e. closer to the testicle) in an operation called an epididymovasostomy. Although this is a technically challenging operation, given improvements in surgical techniques and instrumentation, approximately 60–65% of men will have sperm in the ejaculate following epididymovasostomy.

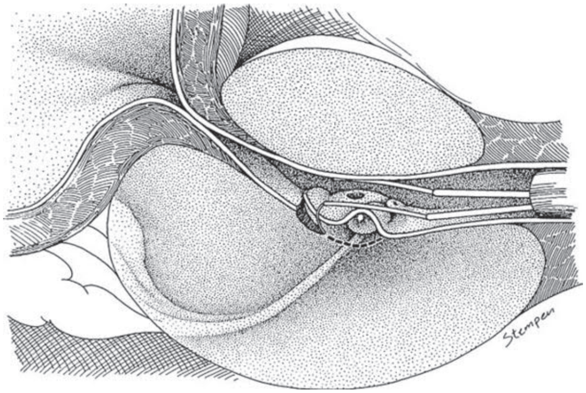
The achievement of sperm in the ejaculate after vasovasostomy depends largely on surgical technique, but pregnancy after surgery is dependent upon the fertility potential of the couple. Therefore, it is critical to understand the reproductive health of the female partner before embarking on the procedure. Other reasons that reproductive tract microsurgery fails are (1) the quality of preblockage semen may not have been normal; (2) ASAs develop in roughly 30% of men who have had vasectomies (high antibody levels may impair fertility); (3) postsurgical scar tissue can develop at the anastomotic site, causing another blockage; and (4) when the vas deferens has been blocked for a long time, the epididymis is adversely affected and sperm maturation may be compromised.

Ejaculatory Duct Obstruction

Ejaculatory duct obstruction EDO) should be suspected when the ejaculate volume is < 1.5 mL and no retrograde ejaculation or hormonal deficit has been identified. EDO can take several forms (Table 44–16). **Complete or classic EDO** is the physical blockage of both ejaculatory ducts and presents with low volume azoospermia. **Incomplete or "partial" EDO** is the unilateral, physical blockage of one of the paired ducts or the partial blockage of both ducts. This condition is generally associated with low ejaculate volume and low sperm concentrations and severely impaired motility. **Functional EDO** is a form of ejaculatory dysfunction that presents as classic EDO but without anatomical evidence of physical blockage. Clinical suspicion can be confirmed by TRUS demonstration of dilated seminal vesicles or dilated ejaculatory ducts. Patients with ejaculatory duct obstruction sufficient to cause coital discomfort, recurrent hematospermia, or infertility should be considered for treatment.

Table 44–16. Classification of ejaculatory duct obstruction by semen analysis parameters.

Parameter	Incomplete or partial	Complete	Functional
Ejaculate volume	Low or low-normal	Low	Low
Sperm count	Low	Absent	Absent or low
Sperm motility	Low	Absent	Absent or low
Ejaculate fructose	Present	Absent	Absent or low



▲ **Figure 44–13.** Transurethral resection of the ejaculatory ducts. A cystoscope with a resecting loop is used to remove the verumontanum and unroof an associated obstructing cyst that has compressed and obstructed the ejaculatory ducts. (Reproduced with permission from Graham SD,m Glenn JF: *Glenn's Urologic Surgery*, 5th ed. Philadelphia, PA: Lippincott; 1998.)

Transurethral resection of the ejaculatory ducts is performed cystoscopically (Figure 44–13). A small resectoscope is inserted, and the verumontanum is resected in the midline until the ducts are visualized. The concomitant use of real-time, transrectal ultrasound may increase the accuracy of resection. Since the area of resection is at the prostatic apex, near the external urethral sphincter and the rectum, careful positioning of the resectoscope is essential. A total of 65–70% of men show significant improvement in semen quality after TURED, and a 30% pregnancy rate can be expected. The complication rate from TURED is approximately 20%. Most complications are self-limited and include hematospermia, hematuria, urinary tract infection, epididymitis, and a watery ejaculate. Rarely reported complications include retrograde ejaculation, rectal perforation, and urinary incontinence.

Electroejaculation

A complete failure of emission and ejaculation occurs most commonly from spinal cord injury (10,000 cases/year in the United States) and as a result of deep pelvic or retroperitoneal surgery that injured the pelvic sympathetic nerves. With rectal probe electroejaculation, the pelvic sympathetic nerves undergo controlled stimulation, with contraction of the vas deferens, seminal vesicle, and prostate, such that a reflex ejaculation is induced. The semen is collected from the penis and the bladder as retrograde ejaculation is often associated with electroejaculation. Semen acquired in this way at minimum requires the use of intrauterine insemination to allow for pregnancy.

In men with anejaculation after retroperitoneal surgery or spinal trauma, successful recovery of sperm with electroejaculation is possible in most patients. Sperm motility tends to be lower than normal when obtained in this way, an effect independent of electrical or heat effects inherent to the procedure. In men with spinal cord injuries above the T5 level, it is often possible to induce a reflex ejaculation with high-frequency penile vibration, termed **vibratory stimulation**. With the use of handheld vibrators set to a frequency of 110 cycles/s (cps) at an amplitude of 3 mm, patients may be taught to perform the procedure and attempt to conceive at home with cervical insemination.

▶ Sperm Retrieval

Sperm retrieval techniques are indicated for men in whom ejaculation of sperm is not possible because the ductal system is absent, surgically unreconstructable, or because the couple has elected to use ART rather than vasectomy reversal. Testicular sperm retrieval is also indicated in men with nonobstructive azoospermia who may harbor areas of reduced spermatogenesis within the testes. Given these widely varied indications, retrieval techniques have evolved to include minimally invasive aspiration procedures and more invasive dissections of the testis with the aid of an operating microscope. Sperm are routinely aspirated from the vas deferens, epididymis, or testicle. It is important to realize that IVF is required to achieve a pregnancy with these procedures. Thus, success rates are intimately tied to a complex program of assisted reproduction for both partners (Table 44–17). In cases of sperm aspiration from the testicle and epididymis, IVF along with ICSI is required. An obvious prerequisite for these procedures is sperm production. Although evaluated indirectly by hormone levels and testis volume, the most direct way to verify sperm production is with a testis biopsy.

A. Vasal Aspiration

After a scrotal incision and with an operating microscope, a hemivasotomy is made, and leaking sperm are aspirated into culture medium. Once enough sperm are obtained (>10–20 million), the vasotomy is closed with microscopic sutures. Vasal aspiration provides the most mature sperm; however, this procedure is rarely performed, given the technical considerations and poor reliability of identifying healthy sperm from the vas.

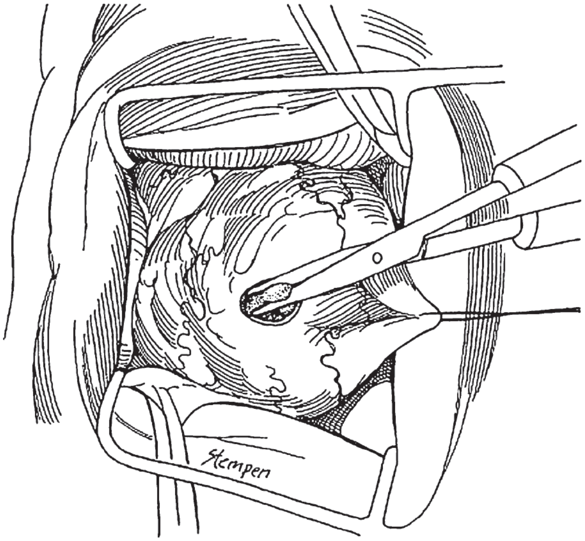
Table 44–17. Sources of retrieved sperm and associated reproductive technologies.

Procedure	Source	IVF	Micromanipulation
Vasal aspiration	Vas deferens	Usually	No
Epididymal aspiration	Epididymis	Yes	Yes
Testis biopsy	Testicle	Yes	Yes

IVF = in vitro fertilization.

B. Epididymal Sperm Aspiration

Epididymal sperm aspiration may be performed by two distinct techniques. With microscopic epididymal sperm aspiration (MESA), sperm are directly collected from a single, isolated epididymal tubule (Figure 44–14). After sperm are obtained, the epididymal tubule may be closed with fine, microscopic suture, and the sperm are processed. When the epididymis is palpable, sperm may also be obtained with percutaneous epididymal sperm aspiration (PESA). Although this technique is a less invasive, the blind insertion of a needle into the epididymis may be more likely to result in tubule injury; however, decreased success of a subsequent vasectomy reversal has not been demonstrated. Epididymal sperm are not as mature as vasal sperm; consequently, epididymal sperm require ICSI to fertilize the egg. Egg fertilization rates of 65% and pregnancy rates of 50% are possible with epididymal sperm, but results vary among individuals owing to differences in sperm and egg quality.



▲ **Figure 44–14.** Microscopic epididymal sperm aspiration. A small "window" incision is made in the scrotum and held open with a small retractor. Under 20× magnification, the epididymis is dissected, and a single epididymal tubule is incised with microscissors. Fluid containing sperm is aspirated for use with in vitro fertilization.

C. Testis Sperm Retrieval

Testicular sperm extraction (TESE) is indicated for patients in whom reconstruction of an obstructed vas or epididymis is either not feasible or not desired, or in cases of severe testis failure, in which so few sperm are produced that they do not reach the ejaculate. Testicular sperm retrieval procedures are highly variable in terms of their surgical invasiveness. Whenever possible, the least invasive approach necessary to acquire adequate sperm should be used. In traditional TESE, a small section of testis tissue is taken in a manner similar to that of a standard testis biopsy. When spermatogenesis is known or suspected to be normal, or is reduced but uniformly distributed throughout the testicle, then testicular sperm aspiration (TESA) should be considered. In distinction to this, if spermatogenesis is markedly reduced, as in many cases of nonobstructive azoospermia, the greatest changes for successful sperm retrieval will achieved by meticulously dissecting all testicular tissue with the aid of a surgical microscope (micro-TESE), with or without a preemptive fine-needle aspiration map. The testis tissue is specially treated in the laboratory to separate sperm from other cells. High egg fertilization rates (60–75%) and pregnancy rates (40–50%) are possible with testis sperm despite the fact that normal motility is usually lacking.

Orchidopexy

An undescended testis occurs in 0.8% of male infants at 1 year of age and the incidence may be increasing. Historically, orchidopexy was done to allow for palpation of a testis that was at increased risk for cancer. More recent evidence suggests that early orchidopexy reduces cancer risk and may improve spermatogenesis later in life. Histologic studies of undescended testis show that significant decreases in spermatogonial numbers occur between birth and 2 years of age. Orchidopexy has been recommended within 2 years of age to potentially prevent this germ cell degeneration. Given that sperm can be retrieved from very atrophic testes and used with assisted reproduction, orchidopexy and not orchiectomy should be the primary goal in these cases.

Torsion of the testis is a urologic emergency. Data from animal studies suggesting that the unaffected, contralateral testis may also develop impaired spermatogenesis termed **sympathetic orchidopathia**. This phenomenon may be immunologic in nature and is the basis for the recommendation that a nonviable torsed testicle be removed at diagnosis. However, given the advances in assisted reproductive technologies, such recommendations should be reconsidered.

Pituitary Ablation

Hyperprolactinemia from a pituitary adenoma can be treated medically and surgically. If the adenoma is radiologically visible (macroadenoma), then transsphenoidal surgical ablation of the lesion is possible. If the adenoma is not visible (microadenoma), then medical therapy with the dopamine agonist bromocriptine or a derivative is more appropriate. Studies have suggested that hyperprolactinemia alone, independent of gonadotropin deficiencies can suppress normal testicular function.

NONSURGICAL TREATMENT

Specific Therapy

Specific therapy in the present context refers to treatments aimed at reversing known pathophysiology in an effort to improve spermatogenesis and fertility. These therapies should be contrasted to empiric therapies that aim to overcome a pathologic condition. Whenever possible, specific therapies should be elected over empiric therapies.

A. Leukocytospermia

Elevated leukocytes in semen is termed **leukocytospermia** and has been associated with (1) subclinical genital tract infection, (2) elevated reactive oxygen species, and (3) poor sperm function and infertility. The treatment of leukocytospermia is controversial in the absence of overt bacteriologic infection. It is important to evaluate the patient for sexually transmitted diseases, penile discharge, prostatitis, or epididymitis. An expressed prostatic secretion is examined for leukocytes, while urine can be assayed for chlamydial, gonococcal, and mycoplasma infections. The use of broad-spectrum antibiotics such as doxycycline and trimethoprim–sulfamethoxazole may reduce seminal leukocyte concentrations or improve sperm function; however, this remains a debated topic. Generally, the female partner is also treated. Importantly, the histologic appearance of immature germ cells can be confused with leukocytes in a semen sample. Therefore, it is critically important to avoid treating leukocytospermia purely on the basis of elevated "round cells." Specific staining for leukocyte esterase with a concentration of cells greater than one million per milliliter confirms the diagnosis.

In cases of confirmed leukocytospermia, frequent ejaculation (more than every 3 days) and doxycycline may result in a more durable resolution than antibiotic treatment alone. There is increasing evidence that the antioxidant vitamins (A, C, and E) as well as glutathione and omega-3 fatty acids (fish oil) may help scavenge reactive-oxygen species within semen and improve sperm motility in cases of leukocytospermia.

B. Coital Therapy

Simple counseling on issues of coital timing, frequency, and gonadotoxin avoidance can improve fertility. It is important to review the essentials of basal body temperature charting or home kits that detect the LH surge in the urine immediately (<24 hours) before ovulation. Since sperm reside in the cervical mucus for 48 hours and are released continuously, it is not necessary that coitus and ovulation occur at the exact same time. In general, coitus every other day around ovulation is an appropriate recommendation. Coital lubricants should be avoided, if possible, as many commercially available products are toxic to sperm. If necessary, vegetable oils, olive oil, and egg whites are the safest.

Retrograde ejaculation results from a failure of the bladder neck to close during ejaculation. Diagnosed by the finding of sperm within the postejaculate bladder urine, it can be treated with sympathomimetic medications. Approximately 30% of men will respond to treatment with some degree of antegrade ejaculation. Begun several days before ejaculation, imipramine (25–50 mg twice a day), or Sudafed Plus (60 mg 3 times per day) have been used with success. For medication failure, sperm-harvesting techniques can be used with IUI to achieve a pregnancy. Premature ejaculation occurs when men ejaculate before the partner is ready. Sexual counseling combined with tricyclic antidepressants or serotoninergic uptake inhibitors can be effective.

C. Immunologic Infertility

Antisperm antibodies are a complex problem underlying male infertility. Available treatment options include corticosteroid immune suppression, sperm washing, IUI, IVF, and ICSI. Steroid suppression is based on the concept that the immune system can be weakened to reduce antibodies on sperm; however, this modality is rarely used given the potential for significant side effects. Intrauterine insemination places more sperm nearer the ovulated egg to optimize the sperm–egg environment. Pregnancy rates with this technique generally fall in the 10–15%/cycle range. Assisted reproductive technology with IVF and ICSI is very effective in this scenario. In general, if >50% of sperm are bound with antibodies, then treatment should be offered. In addition, head-directed or midpiece-directed sperm antibodies appear more relevant than tail-directed antibodies.

D. Medical Therapy

Hormone therapy is effective when it is used as specific and not empiric treatment. Specific replacement therapy seeks to reverse well-established pathophysiologic states. Empiric treatments attempt to overcome pathologic conditions that are ill-defined or have no proven treatment.

1. Hyperprolactinemia—Normal levels of prolactin in men help sustain high intratesticular testosterone levels and affect the growth and secretions of the accessory sex glands. Hyperprolactinemia abolishes gonadotropin pulsatility by interfering with episodic GnRH release. Visible lesions are generally treated with transsphenoidal surgery, and nonvisible lesions are treated with bromocriptine, 5–10 mg daily, to restore normal pituitary balance.

2. Hypothyroidism—Both elevated and depressed levels of thyroid hormone can impair spermatogenesis. Replacement or removal of low or excessive thyroid hormone is effective treatment for infertility. As these diseases are clinically evident, routine thyroid screening is not recommended for infertility patients.

3. Congenital adrenal hyperplasia—Most commonly, the 21-hydroxylase enzyme is deficient resulting in cortisol deficiency and excess androgen production. The testes fail to mature because of gonadotropin inhibition, due to the presence of excessive androgens. The diagnosis is rare and classically presents as precocious puberty; careful laboratory evaluation is essential. In both sexes, the condition and the infertility associated with it are treated with corticosteroids.

4. Testosterone excess/deficiency—Patients with Kallmann syndrome lack GnRH that stimulates normal pituitary function. Infertility associated with this condition can be very effectively treated with hCG, 1000–2000 U 3 times weekly, and recombinant FSH 75 IU twice weekly, to replace LH and FSH. It is also possible to give GnRH replacement in a pulsatile manner, 25–50 ng/kg every 2 hours, by a portable infusion pump. Individuals with fertile eunuch syndrome or isolated LH deficiency respond well to hCG therapy alone. One can expect to find sperm in the ejaculate beginning 9–12 months after therapy is started. Since injectable drug regimens are long, complex, and costly, it is good practice for men to cryopreserve motile sperm once achieved in the ejaculate. Anabolic steroids are a common and underdiagnosed reason for testicular failure in which excess exogenous testosterone and metabolites depress the pituitary–gonadal axis and spermatogenesis. Initially, the patient should discontinue the offending hormones to allow the return of normal homeostatic balance. Second-line therapy generally consists pituitary stimulation with clomiphene citrate (see text below) or with testis stimulation with hCG and FSH as with the Kallmann syndrome.

▶ Empiric Medical Therapy

Nearly a quarter of men evaluated for infertility will not have an identifiable cause. Because the pathophysiology is ill-defined, this is termed **idiopathic infertility**. Additionally, other men in whom an abnormality is identified on semen analysis may have no specific target for therapy. Both groups of men are candidates for empiric medical therapy. This form of therapy seeks to overcome pathologic conditions that are ill-defined or have no proven treatment. As a rule, it is important to establish a timeline of therapy and decide with the patient when empiric treatment is to be discontinued and other avenues pursued.

A. Clomiphene Citrate

Clomiphene citrate is a synthetic, nonsteroidal antiestrogen that blocks the action of the normally low levels of estrogen on the male hormone axis, resulting in increased secretion of GnRH, FSH, and LH. The enhanced output of these hormones generally increases testosterone production and may improve spermatogenesis. Its use in male infertility treatment is "off-label," as it is only FDA-approved for the treatment of female infertility. Clomiphene therapy is given for idiopathic low sperm count in the setting of low-normal LH, FSH, and testosterone levels. The dose is 12.5–50 mg/day either continuously or with a 5-day rest period each month. Serum gonadotropins and testosterone should be monitored at 3 weeks and the dose adjusted to keep the testosterone level within the normal range. Higher than normal testosterone levels may result in hyperestrogenemia and decreased semen quality. Therapy should be discontinued if no semen quality response is observed in 6 months. Although there have been over 30 published trials on clomiphene since 1964, only a few include control arms. In general, the results of these studies have been equivocal in terms of the effectiveness of clomiphene citrate as an empiric therapy. Recent data have suggested that treatment of nonobstructive azoospermic men with clomiphene citrate may improve the odds of successful surgical sperm retrieval.

B. Antioxidant Therapy

There is evidence that up to 40% of infertile men have increased levels of reactive oxygen species in the reproductive tract. These species (OH, O_2 radicals, and hydrogen peroxide) can cause lipid peroxidation damage to sperm membranes that leads to deficits in sperm motility and overall function. Treatment with scavengers of these radicals may protect sperm from oxidative damage. Proposed agents have included glutathione, vitamin E, and fish oil. These agents may be useful in a subgroup of infertile men with elevated levels of seminal reactive oxygen species. Unfortunately well-controlled studies demonstrating the effectiveness of these supplements are small or not available.

ASSISTED REPRODUCTIVE TECHNOLOGIES

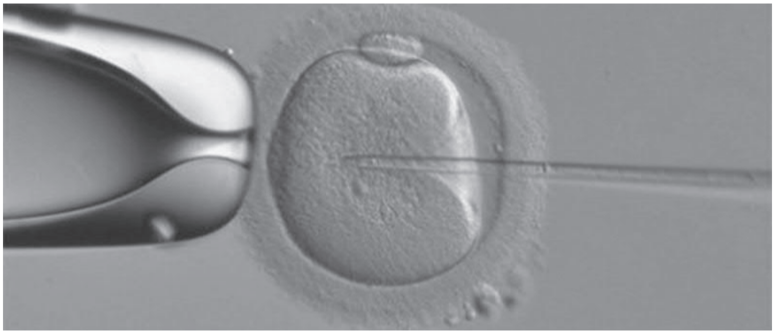
If neither surgery nor medical therapy is appropriate for male infertility treatment, assisted reproductive techniques can be used to achieve a pregnancy. Generally speaking, ARTs represents the most profound implementation of empiric therapies.

Intrauterine Insemination (IUI)

Intrauterine insemination represents the least technological of all ARTs and is generally classified separately from in vitro fertilization. IUI involves the placement of a washed pellet of ejaculated sperm beyond the cervix, within the female uterus. The specific indication for IUI is for a cervical factor; if the cervix is bypassed, then pregnancies may ensue. IUI is also used for low sperm quality, for immunologic infertility, and in men with mechanical problems of sperm delivery (eg, hypospadias). IUI is commonly used for idiopathic infertility. There should be at least 5 million motile sperm in the ejaculate (volume × concentration × motility) to make this procedure worthwhile. Success rates vary widely and are directly related to female reproductive potential; given this, pregnancy rates of 8–16% per cycle have been reported with IUI as a treatment for male infertility. Success rates are improved if the female partner is treated with medication to stimulate ovulation.

In Vitro Fertilization and ICSI (Figure 44–15)

In vitro fertilization involves controlled ovarian stimulation and ultrasound-guided transvaginal egg retrieval from the ovaries before normal ovulation occurs. Eggs are then combined with washed sperm in petri dishes to allow fertilization to occur. Importantly, significant numbers of post-wash, motile sperm (ranging from 500,000 to 5 million) are necessary for traditional IVF to be successful. In 1992, microscopic injection of a single sperm into the subzonal space of an egg to cause a pregnancy was described. This technology, termed intracytoplasmic sperm injection (ICSI), has revolutionized the treatment of severe male factor infertility. The sperm requirement for egg fertilization has dropped from hundreds of thousands for IVF to 1 viable sperm for ICSI. This has led



▲ **Figure 44–15.** The intracytoplasmic sperm injection procedure. (***Top***) A mature oocyte (*left*) is readied for injection with a sperm (*arrow*) in a micropipette under the microscope. (***Bottom***) The micropipette is placed directly into the oocyte, and the sperm is deposited into the cytoplasm.

to the development of aggressive new surgical techniques to provide sperm for egg fertilization from azoospermic men azoospermia. The availability of these techniques has pushed urologists to look beyond the ejaculate and into the male reproductive tract to find sperm for biologic pregnancies. At present, sources of sperm include the vas deferens, epididymis, and testicle. Since IVF and ICSI eliminate many natural selection barriers that exist during natural fertilization, genetic defects that caused the infertility are expected to be passed on to offspring. Because ICSI is a relatively new technique, long-term data concerning future health and fertility of children conceived with ICSI are not yet available. Some studies have reported the increased incidence of hypospadias in babies conceived through ICSI. Further, because some causes of male infertility are familial and related to genetic problems (Y microdeletions), male offspring may also suffer from impairments in spermatogenesis, inherited from their fathers.

▶ Preimplantation Genetic Diagnosis or Screening

Preimplantation genetic diagnosis is a specialized technique that enables the laboratory to precisely define the genetic normality of embryos. In patients with heritable, possibly life-threatening diseases, it is possible that offspring conceived with IVF and ICSI may have these diseases transmitted to them. This complex technique involves the removal of single cells from the early embryo while it is grown in petri dishes before transfer to the uterus. The genetic material from these "biopsied" cells can then be examined to determine whether the embryo carries an abnormal chromosome or gene. Through preimplantation genetic diagnosis, early human embryos that result from IVF and ICSI can be examined individually as they develop for the presence or absence of suspected genetic traits. Because of the real-time nature of the technique, decisions regarding embryo transfer are made within 24 hours and help ensure that lethal diseases are not transmitted to offspring. Remarkably, the removal of a few cells from the embryo is not detrimental to the survival and normal development of most embryos.

▶ Nonreproductive Implications of Male Infertility

Beyond the significant psychosocial and marital stress associated with male infertility, several epidemiologic studies have suggested that male infertility may be a marker for overall health. A large, longitudinal Danish study suggested that male fertility may be associated with overall longevity, whereby men with better semen quality may lower age-adjusted mortality than men with worse semen quality. Other studies have demonstrated that male infertility is a strong risk factor for the development of testicular germ cell cancer later in life. A large US cohort study found that infertile men were nearly 3 times more likely to develop testis cancer, and on average, that men presented with infertility more than a decade prior to developing cancer. Other studies have suggested that male subfertility may be a risk factor for prostate cancer; however, these studies have yet to be confirmed, and further investigation is warranted. While male infertility and its treatments are unlikely to cause cancer, it is highly likely that these diseases share a common underlying etiology. Given that men present with reproductive failure relatively early in life, the epidemiologic study of infertile men may provide the opportunity to identify and remove exposure to carcinogenic agents.

BIBLIOGRAPHY

Male Reproductive Physiology

Aitken RJ, West K, Buckingham D: Leukocytic infiltration into the human ejaculate and its association with semen quality, oxidative stress, and sperm function. J Androl 1994;15:343. [PMID: 7982803]

Gui YL et al: Male hormonal contraception: Suppression of spermatogenesis by injectable testosterone undecanoate alone or with levonorgestrel implants in Chinese men. J Androl 2004;25:720. [PMID: 15292101]

Hess RA et al: A role for estrogens in the male reproductive system. Nature 1997;390:509. [PMID: 9393999]

Von Eckardstein S et al: Serum inhibin B in combination with FSH is a more sensitive marker than FSH alone for impaired spermatogenesis in men, but cannot predict the presence of sperm in testicular tissue samples. J Clin Endocrinol Metab 1999;2496. [PMID: 0404826]

Evaluation of Male Infertility

Agarwal A et al: Clinical relevance of oxidative stress in male factor infertility: An update. Am J Reprod Immunol 2008;59:2. [PMID: 18154391]

Carlsen E et al: Evidence for decreasing quality of semen during the past 50 years. Br Med J 1992;105:609. [PMID: 1393072]

Carlsen E et al: History of febrile illness and variation in semen quality. Hum Reprod 2003;18:2089. [PMID: 14307826]

Chemes HE: Phenotypes of sperm pathology: Genetic and acquired forms in infertile men. J Androl 2000;21:799. [PMID: 11105905]

Gandini L et al: Effect of chemo- or radiotherapy on sperm parameters of testicular cancer patients. Hum Reprod 2006;21:2882. [PMID: 16997940]

Clifton DK, et al: The effect of testicular X-irradiation on spermatogenesis in man: A comparison with the mouse. J Androl 1983;4:387. [PMID: 6654753]

Eisenberg ML et al: Semen quality and pregnancy loss in a contemporary cohort of couples recruited before conception: Data from the Longitudinal Investigation of Fertility and the Environment (LIFE) study. Fertil Steril 2017;108(4):613–619. [PMID: 28863939]

Guzick DS et al: Sperm morphology, motility and concentration in fertile and infertile men. New Engl J Med 2001;343:1388. [PMID: 11794171]

Hammoud AO et al: Impact of male obesity on fertility: A critical review of the current literature. Fertil Steril 2008;90:897. [PMID: 18929048]

Jarow JP et al: Male Infertility Best Practice Policy Committee of the American Urological Association Inc. J Urol 2002;167:2138. [PMID: 11956464]

Kruger TF et al: Predictive value of abnormal sperm morphology in vitro fertilization. Fertil Steril 1988;49:112. [PMID: 3335257]

Meinertz H et al: Antisperm antibodies and fertility after vasovasostomy: A follow-up study of 216 men. Fertil Steril 1990;54:315. [PMID: 2379630]

Sallmen M et al: Reduced fertility among overweight and obese men. Epidemiology 2006;17:520. [PMID: 16837825]

Sigman M, et al: Medical evaluation of infertile men. Urology 1997;50:659. [PMID: 9372871]

Smith JF, et al: Ejaculatory duct obstruction. Urol Clin North Am 2008; 35(2):221 [PMID: 18423242]

Turek PJ et al: Diagnostic findings from testis fine needle aspiration mapping in obstructed and non-obstructed azoospermic men. J Urol 2000;163:1709. [PMID: 10799166]

Turek PJ: Practical approach to the diagnosis and management of male infertility. Nature Clin Pract Urol 2005;2:1.

Urban MD, et al: Adult height and fertility in men with congenital virilizing adrenal hyperplasia. New Engl J Med 1978;299:1392. [PMID: 152409]

World Health Organization: WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 4th ed. Cambridge University Press, 1999. pp. 60–61.

Xu WM et al: Cystic fibrosis transmembrane conductance regulator is vital to sperm fertilizing capacity and male fertility. Proc Natl Acad Sci USA 2007;104(23):9816. [PMID: 17873061]

Zini A et al: Prevalence of abnormal sperm DNA denaturation in fertile and infertile men. Urology 2002;60:1069. [PMID: 12475672]

Causes of Male Infertility

Pretesticular

Aiman J et al: Androgen insensitivity as a cause of infertility in otherwise normal men. New Engl J Med 1979;300:223. [PMID: 7598691]

Carter JN et al: Prolactin-secreting tumors and hypogonadism in 22 men. New Engl J Med 1978;299:847. [PMID: 211411]

Fujisawa M et al: Growth hormone releasing hormone test for infertile men with spermatogenetic maturation arrest. J Urol 2002;168:2083. [PMID: 12394714]

Goffin V et al: Prolactin: The new biology of an old hormone. Ann Rev Physiol 2002;64:47. [PMID: 11826263]

Griffin JE: Androgen resistance: The clinical and molecular spectrum. New Engl J Med 1992;326:611. [PMID: 1734252]

Oliveira LMB et al: The importance of autosomal genes in Kallmann syndrome: Genotype-phenotype correlations and neuroendocrine characteristics. J Clin Endocr Metab 2001;86:1532. [PMID: 11297579]

Wu SM, et al: Male pseudohermaphroditism due to inactivating luteinizing hormone receptor mutations. Arch Med Res 1999;30: 495. [PMID: 10714363]

Testicular

Aiman J, et al: The frequency of androgen receptor deficiency in infertile men. J Clin Endocrinol Metab 1982;54:725. [PMID: 6801070]

Hopps CV et al: Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions. Hum Reprod 2003;18,1660. [PMID: 12871878]

Kostiner DR, et al: Male infertility: Analysis of the markers and genes on the human Y chromosome. Hum Reprod 1998;13:3032. [PMID: 9853850]

Lipshultz LI et al: Testicular function after orchiopexy for unilaterally undescended testis. New Engl J Med 1976;295:15. [PMID: 5671]

Nagler HM, et al: Testicular torsion: Temporal considerations. Fertil Steril 1984;42:257. [PMID: 6743439]

Richardson I et al: Outcomes of varicocele treatment: An updated critical analysis. Urol Clin North Am 2008;35:191. [PMID: 18423240]

Walsh TJ et al: Prepubertal orchidopexy for cryptorchidism may be associated with lower risk of testicular cancer. J Urol 2007;178:1430. [PMID: 17706709]

Walsh TJ et al: Differences in the clinical characteristics of primarily and secondarily infertile men with varicocele. Fertil Steril 2009;91: 826 [PMID: 18314114]

World Health Organization: The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. Fertil Steril 1992;57:1289. [PMID: 1601152]

Posttesticular

Chillon M et al: Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. New Engl J Med 1995;332:1475. [PMID: 7739684]

Handelsman DJ et al: Young's syndrome: Obstructive azoospermia and chronic sinopulmonary infections. New Engl J Med 1984;310:3. [PMID: 6689737]

Matsuda T, et al: Obstructive azoospermia of unknown origin: Sites of obstruction and surgical outcomes. J Urol 1994;151:1543. [PMID: 8189567]

Genetic Causes of Male Infertility

Anguiano A et al: Congenital bilateral absence of the vas deferens: A primarily genital form of cystic fibrosis. JAMA 1992;267:1794. [PMID: 1543465]

Kenti-First MG et al: Infertility in intracytoplasmic-sperm-injection-derived sons. Lancet 1996;348:332. [PMID: 8709700]

Kurda-Kawaguchi T et al: The AZFc region of the Y chromosome features massive palindromes and uniform recurrent deletions in infertile men. Nat Genet 2001;29:279. [PMID: 11687796]

Pryor JL et al: Microdeletions in the Y chromosome of infertile men. New Engl J Med 1997;336:534. [PMID: 9023089]

Reijo R et al: Diverse spermatogenic defects in humans caused by Y chromosome deletions encompassing a novel RNA-binding protein gene. Nat Genet 1995;10:383. [PMID: 7670487]

Walsh TJ et al: The genetics of male infertility. Semin Reprod Med 2009; 27(2):124. [PMID: 19247914]

Xu EY, et al: A gene family required for human germ cell development evolved from an ancient meiotic gene conserved in metazoans. Proc Natl Acad Sci (USA) 2001;98:7414. [PMID: 11390979]

Treatment

Baker WHG et al: Protective effect of antioxidants on the impairment of semen motility by activated polymorphonuclear leukocytes. Fertil Steril 1996;65:411. [PMID: 8566272]

Belker AM et al: Results of 1,469 microsurgical vasectomy reversals by the vasovasostomy study group. J Urol 1991;143:505. [PMID: 1997700]

Bennett CJ et al: Sexual dysfunction and electroejaculation in men with spinal cord injury: Review. J Urol 1988;139:433. [PMID: 3278126]

Branigan EF, Muller CH: Efficacy of treatment and recurrence rate of leukocytospermia in infertile men with prostatitis. Fertil Steril 1994;62:580. [PMID: 7520396]

Cayan S et al: Can varicocelectomy significantly change the way couples use assisted reproductive technologies? J Urol 2002;167:1749. [PMID: 11912402]

Cayan S et al: Response to varicocelectomy in oligospermic men with and without defined genetic infertility. Urology 2001;57:530. [PMID: 11248633]

Cox G et al: Intracytoplasmic sperm injection may increase the risk of imprinting defects. Am J Hum Genet 2002;71:162. [PMID: 12016591]

Damani MN et al: Post-chemotherapy ejaculatory azoospermia: Fatherhood with sperm from testis tissue using intracytoplasmic sperm injection. J Clin Oncol 2002;20:930. [PMID: 11843813]

DeBaun M, Niemitz E, Feinberg A: Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. Am J Hum Genet 2003;72:156. [PMID: 12439823]

Eisenberg ML et al: Ejaculatory duct manometry in normal men and in patients with ejaculatory duct obstruction. J Urol 2008;180:255. [PMID: 18499178]

Eisenberg ML et al: Racial differences in vasectomy utilization in the United States: Data from the national survey of family growth. Urology 2009;74:1020. [PMID 19773036]

Evers JLH, Collins JA: Assessment of efficacy of varicocele repair for male subfertility: A systematic review. Lancet 2003;361:1849. [PMID: 12788571]

Fuchs EF, Burt RA: Vasectomy reversal performed 15 years or more after vasectomy: Correlation of pregnancy outcome with partner age and with pregnancy results of in vitro fertilization with intracytoplasmic sperm injection. Fertil Steril 2002;77:516. [PMID: 11872205]

Guzick DS et al: Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. New Engl J Med 1999;340:177. [PMID: 9895397]

Kadioglu A et al: Does response to treatment of ejaculatory duct obstruction in infertile men vary with pathology? Fertil Steril 2001;76:138. [PMID: 11438332]

Madgar I et al: Controlled trial of high spermatic vein ligation for varicocele in infertile men. Fertil Steril 1995;63:120. [PMID: 7805900]

Matthews GJ, Schlegel PN, Goldstein M: Patency following microsurgical vasoepididymostomy and vasovasostomy: Temporal considerations. J Urol 1993;154:2070. [PMID: 7500460]

Meng M, Green K, Turek PJ: Surgery or assisted reproduction? A decision analysis of treatment costs in male infertility. J Urol 2005;174:1926. [PMID: 16217347]

Patel DP et al: The safety and efficacy of clomiphene citrate in hypoandrogenic and subfertile men. Int J Impot Res 2015;27(6):221–224 (doi: 10.1038/ijir.2015.21; Epub 8/20/15). [PMID: 26289907]

Yang G et al: The kinetics of the return of motile sperm to the ejaculate after vasectomy reversal. J Urol 2007;177.

Nonreproductive Implications of Male Infertility

Glazer CH et al: Male infertility and risk of nonmalignant chronic diseases: A systematic review of the epidemiological evidence. Semin Reprod Med 2017;35(3):282–290. [PMID: 28658712]

Hanson BM et al: Male infertility: A biomarker of individual and familial cancer risk. Fertil Steril 2018;109(1):6–19.

Walsh TJ et al: Increased risk of testicular germ cell cancer among infertile men. Arch Int Med 2009;169(4):351. [PMID: 19237718]

This page intentionally left blank

The Aging Male

45

James F. Smith, MD, MS; Bogdana Schmidt, MD, MPH; &
Thomas J. Walsh, MD, MS

INTRODUCTION

The proportion of individuals older than 65 years is expected to rise significantly over the next 25 years. According to US census data, the number of Americans older than 65 years will rise to nearly 55 million in 2020 (16.3% of total), and nearly 87 million in 2050 (20.7% of total). Consequently, the healthcare system will likely experience a dramatic increase in age-related health problems, such as cancer, cerebrovascular and ischemic heart disease, and hypogonadism. A substantial body of literature supports the assertion that hormonal changes in the aging male can be associated with significant health problems. This chapter reviews the epidemiology of age-related hypogonadism; alterations in testis biology that occur with age; and the effects that these changes may have on semen quality, fertility, birth defects in offspring, and on the overall health of older men.

EPIDEMIOLOGY

Hypogonadism is a clinical syndrome in men with symptoms and signs of testosterone deficiency and low serum testosterone concentration. From a population standpoint, the effect of aging on circulating testosterone levels is highly significant. The Baltimore Longitudinal Study of Aging (BLSA) found that 12%, 20%, 30%, and 50%, respectively, of men in their fifties, sixties, seventies, and eighties were hypogonadal using a total serum testosterone threshold of 325 ng/dL. More recently, testosterone trials of men aged ≥65 years used a more stringent serum testosterone threshold of 275 ng/dL, and screened 51,085 men to enroll 790, for an inclusion rate by testosterone level of 14.7%. Age has been shown to be an independent risk factor for hypogonadism even after adjustment for chronic medical conditions, such as obesity, diabetes mellitus, and hyperthyroidism.

CHANGES IN TESTIS BIOLOGY WITH AGE

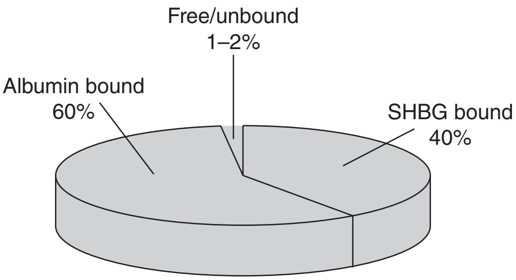
▶ Endocrine Testis

A. Leydig Cells

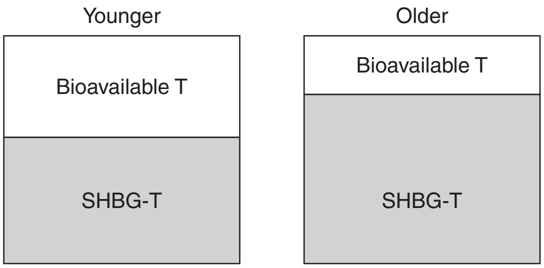
The quest to understand the underlying mechanism behind the epidemiological and clinical observation that aging men experience a gradual decline in testosterone levels led to the analysis of Leydig cell populations in human testes. Leydig cells produce 95% of adult male testosterone and are found in the interstitial space between seminiferous tubules. Kaler and Neaves (1978), in a study of testes retrieved at autopsy after sudden death among men aged 18–87, noted that total Leydig cell volume declines significantly with age and that decline is directly proportional to a fall in the total number of Leydig cells. From such studies, it is estimated that a pair of young testes (20-year-old) contains 700 million Leydig cells and undergoes an attrition of about 80 million cells per decade of life. Other studies have also shown that serum luteinizing hormone (LH) levels are significantly higher in older men compared with younger men, providing physiologic corroboration of the Leydig cell studies.

B. Testosterone

Although the decline of testosterone levels in older males has been described by the terms andropause, male climacteric, male menopause, late-onset hypogonadism (LOH), and partial androgen deficiency in the aging male (PADAM), or simply “hypogonadism.” Serum testosterone levels in men fall progressively from the third decade to the end of life, primarily due to the decline in testicular Leydig cell mass. This decline may be associated with changes in the circadian rhythm and hypothalamic–pituitary homeostatic control of LH secretion, which regulates testosterone production. Thus,



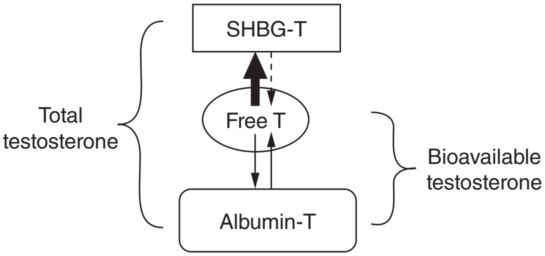
▲ **Figure 45–1.** Relative amounts of various forms of testosterone in the blood. Albumin-bound testosterone is considered "bioavailable" and has physiologic activity, but the SHBG-bound testosterone is chemically unavailable. SHBG, sex hormone-binding globulin.



▲ **Figure 45–3.** Changes in sex hormone-binding globulin (SHBG) with age. Although total testosterone levels may be similar in younger and older men, there is less "available" testosterone due to an increase in SHBG with age. T, testosterone.

mechanisms exist both at the testicular and hypothalamic–pituitary axis levels, which may result in decreased testosterone with age.

Testosterone exists in several different forms in plasma, with each having different bioactivity (Figure 45–1). Free or unbound testosterone is fully bioavailable, but protein-bound testosterone is only partly bioavailable. Among protein-bound forms, albumin-bound testosterone is more freely bioavailable than sex hormone-binding globulin (SHBG)-bound testosterone, which is considered an inactive form of testosterone (Figure 45–2). Population-based studies have demonstrated that aging and several medical comorbidities are associated with an increase in SHBG. This increase in SHBG leads to increased binding to and inactivation of testosterone, lowering the levels of bioavailable androgens (Figure 45–3). Fifty percent of men older than 60 years have below-normal levels of non-SHBG-bound testosterone. The age-related onset, rate, and degree of change in testosterone production are all variable; however, a general rule of thumb is that mean testosterone levels decrease approximately 1% annually after the age of 50 years. Indeed, the concentration of bioavailable testosterone in men decreases by as much as 50% between the ages of 25 and 75 years. In contrast, estradiol and dihydrotestosterone (DHT)—a primary metabolite of testosterone and potent androgen—show minimal declines as men age.



▲ **Figure 45–2.** Diagram outlining the various forms of testosterone in the blood. Total testosterone includes all forms of the hormone, both free and bound. The affinity of sex hormone-binding globulin (SHBG) for testosterone is much higher (*thick arrow*) than that of albumin. Available forms of testosterone that exert physiologic activity include free and albumin-bound fractions. T, testosterone.

▶ The Exocrine Testis

▶ Sertoli Cells

Age-related declines in Sertoli cells have been observed in anatomical studies. These studies revealed that young adult testes have approximately 500 million Sertoli cells compared with 300 million for older men (Table 45–1). Concurrent declines in testicular mass and the numbers of round spermatids have also been observed.

Table 45–1. Comparison of Sertoli cells and germ cells in younger and older men.

	Age range	
Testis parameter	**20–48 years**	**50–85 years**
Average testis weight	19 g	16 g
Number of Sertoli cells/testis	503 million	312 million
Number of round spermatids	55 million/g testis	41 million/g testis
Number of spermatids/ Sertoli cell	4.0	4.3

Data from Johnson L, Zane RS, Petty CS, et al: Quantification of the human Sertoli cell population: Its distribution, relation to germ cell numbers, and age-related decline. Biol Reprod. 1984 Nov;31(4):785–95.

SPERMATOGENESIS

Production

The changes that occur in the seminiferous tubules with age include a decrease in total volume of the testis occupied by seminiferous tubules and a decrease in tubule length. Calculations of mature sperm production in testis tissue homogenates also suggest that daily sperm production decreases significantly with age (Table 45–2). The age-related decrease in sperm production in older testes appears to result from a decrease in primary spermatocytes or a decrease in spermatogonial proliferation rather than cellular degeneration. Correspondingly, follicle-stimulating hormone (FSH) levels increase significantly with age, with mean values threefold higher in older men than in younger men.

Semen Quality

Although an age-related decrease in semen quality might be expected from calculated changes in testis biology with age, this has not been obviously demonstrated clinically. Cross-sectional studies have observed both decreased and unchanged ejaculated sperm concentrations in older versus younger men. However, most studies show that sperm motility is consistently lower in older men compared with younger men, with a decrease of approximately 0.7% motility per year after the third decade. These declines can be difficult to attribute to age, given the wide variability in semen analysis results between repeated samples from the same individual and the lack of prospective, population-based studies to confirm the findings found in cross-sectional analyses.

Fertility

The effect of paternal age on fertility is controversial. Studies that address this issue are confounded by the variables of the aging female partner and decreased coital frequency that occurs with age. Despite these limitations, several studies have demonstrated delays in the time to achieve a pregnancy in men older than 35 years compared with men younger than 30 years, even after controlling for maternal age. Advancing paternal age has also been implicated as a risk factor for developmental and chromosomal abnormalities in their offspring. Increased sperm DNA fragmentation, single gene mutations, and sperm chromosome abnormalities have all been associated with advanced paternal age. Furthermore, there is also an increased risk of miscarriage, fetal loss, and congenital abnormalities in offspring. The mechanism of these changes is not yet clear; however, researchers have demonstrated that increased levels of reactive-oxygen species are found in the semen of older men in addition to higher levels of genetic abnormalities.

Table 45–2. Age-related changes in seminiferous tubules and sperm production.

Testis parameter	Age range	
	20–48 years	50–90 years
Paired testis weight	41 g	31 g
Seminiferous tubule volume	24 mL/person	18 mL/person
Daily sperm production	250 million	121 million

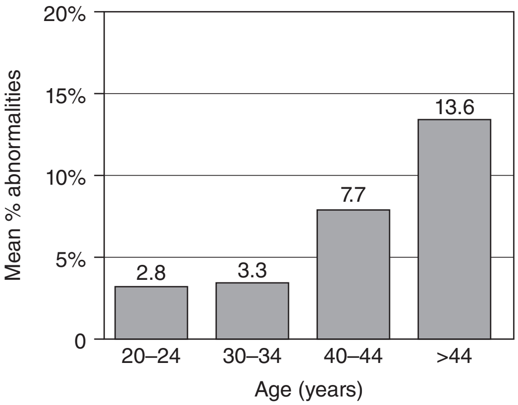
Data from Johnson L, Petty CS, Neaves WB: Age-related variation in seminiferous tubules in men. A stereologic evaluation, J Androl 1986 Sep-Oct;7(5):316–322.

Genetics

A. Sperm Chromosomal Anomalies

Early sperm cytogenetic studies in fertile men stratified by age showed a 10% overall incidence of sperm chromosomal abnormalities, but no relationship between paternal age and the frequency of numerical abnormalities (aneuploidy) in sperm chromosomes. Studies using more sensitive fluorescence in situ hybridization (FISH) technology have shown paternal age effects on sperm aneuploidy. Paternal age appears to increase the fraction of sperm with sex chromosomal aneuploidies, with mixed relative risk results for chromosomes 1, 13, 18, 21, and X (eg, 47,XXY Klinefelter syndrome) in addition to XYZ aberrations. Even more pronounced is the highly significant positive, linear relationship demonstrated between paternal age and the frequency of structural anomalies in sperm (*r* = .63; Figure 45–4).

It is possible that continued cell divisions that characterize spermatogenesis place the germ cells at risk for chromosomal injury, especially given the extended exposure to clastogens,



▲ **Figure 45–4.** **Incidence of sperm chromosomal structural anomalies by paternal age.** (Data from Martin RH, Rademaker AW: The effect of age on the frequency of sperm chromosomal abnormalities in normal men, Am J Hum Genet 1987 Sep;41(3):484–492.)

such as reactive oxygen species, that occur with age. However, it is important to realize that studies of live newborns or prenatally diagnosed fetuses do not support the assertion that de novo structural chromosomal anomalies, with the exception of inherited reciprocal translocations, are found more commonly in the offspring of older men.

B. Sperm Genetic Mutations

Single gene defects in sperm can result from errors in the DNA replication process. Numerous studies have cataloged the association between advanced paternal age and new cases of conditions associated with single gene deletions (Table 45–3). One mechanism for the development of new single gene mutations with advanced paternal age implicates the characteristic and continuous process of spermatogonial cell division in spermatogenesis. By puberty, 30 cell divisions of spermatogonia have occurred, resulting in a large pool of undifferentiated cells. After puberty, 23 divisions per year occur; in a 35-year-old man, these cells will have undergone 540 divisions. The simple fact that the spermatogonial stem cells of older men having undergone numerous cell divisions may make them more likely to contain errors in DNA transcription, the source of single gene defects. The rate of de novo mutations strongly correlates with paternal age, and a generated model predicts that paternal germ-line mutations double every 16.5 years. This finding was confirmed in a study of 11,020 de novo mutations that demonstrated that relative to 20-year-old fathers, 40-year-olds had twice the rate of mutations.

C. Paternal Age and Birth Defects and Disease in Offspring

There is little doubt regarding the association between advanced paternal age and an increased probability of autosomal-dominant diseases in offspring (Table 45–3). This risk of autosomal mutations due to advanced paternal age has been quantified by investigators who demonstrated that for men aged 40–44 years, the risk of a mutation occurring in offspring is 4.5 per 1000 births compared with 0.22 per 1000 births among men younger than 29 years. Analogously, aneuploid conceptions associated with female age demonstrate a similar pattern. It has been suggested that this underlying genetic mechanism may explain the consistent association between paternal age and schizophrenia found among offspring from a range of countries around the world.

There is a reported association between advanced paternal age and malignancy. There has been a reported increased risk for breast cancer, particularly in premenopausal women, associated with advanced paternal age, controlling for maternal age. Women whose fathers were older than 40 years had a 1.6-fold increased risk of breast cancer, compared with fathers younger than 30 years.

There have also been several studies reporting a small increased risk of childhood leukemia.

The association between paternal age and anatomic birth defects has been the source of several studies. One demonstrated that paternal age older than 40 years was associated with a 20% relative increase in the incidence of having offspring with a serious birth defect, such as situs inversus, atrial septal defects, or ventricular septal defects; however, the absolute percentage increased risk of increased age remained small. Another population-based retrospective cohort study demonstrated the baseline rate of birth defects at 1.5%, with a 15% increased risk in paternal age greater than 50 years old. Because of these relationships, guidelines for sperm donors recommend that donors be younger than 40 years.

Table 45–3. Selected genetic disorders associated with advanced paternal age.

Achondroplasias	Aniridia
Apert syndrome	Bilateral retinoblastoma
Crouzon syndrome	Fibrodysplasia ossificans
Hemophilia A	Lesch–Nyhan syndrome
Marfan syndrome	Neurofibromatosis
Oculodentodigital syndrome	Polycystic kidney disease
Polyposis coli	Progeria
Treacher–Collins syndrome	Tuberous sclerosis
Waardenburg syndrome	

DIAGNOSIS OF ANDROGEN DEFICIENCY

Organ System Effects of Testosterone

Testosterone affects a varied number of target organs. In the brain, it may modulate or influence aspects of cognition, mood, sexual interest (ie, libido), and male aggression. Cognitively, verbal memory, visuospatial skills, and memory have been improved in older men taking testosterone replacement therapy. Testosterone stimulates production of erythropoietin and stem cells in the kidney and bone marrow, while in bone, testosterone causes accelerated linear growth and closure of epiphyses for prepubertal males. Testosterone is responsible for an increase in muscle strength and growth. Among young males, testosterone allows for maturation of sexual organs and penile growth. In postpubertal males, endogenous testosterone enhances spermatogenesis and supports prostatic growth and function. The male external appearance is influenced by testosterone as it induces specific body hair growth patterns, temporal balding, and other secondary sex characteristics. Consequently, normal male growth, maturation, and reproductive and sexual function are strongly influenced by testosterone levels (Table 45–4).

In 2002, the National Institute on Aging and the United States National Cancer Institute charged the Institute of

Table 45–4. Testosterone effects in the normal male.

Target organ	Effects
Male sex organs	Growth, development, maintenance of secondary sex characteristics, sperm production, erections, and prostatic function
Behavior	Improved libido, mood, memory, and energy
Bone	Linear growth, closure of the epiphyses, and increased bone mineral density
Fat tissue	Body and visceral fat reduction
Muscle	Anabolic; increases muscle mass and possibly strength
Liver	Stimulates production of serum proteins
Kidney	Stimulates erythropoietin production
Heart	Causes coronary vasodilation
Blood	Suppression of clotting factors (II, V, VII), low HDL cholesterol
Bone marrow	Stimulates stem cell production
Hair	Influences body hair growth, especially facial hair

Medicine (IOM) with conducting an analysis of the effects of testosterone replacement in aging men. This report summarized many of the effects that testosterone treatment has on a wide range of organ systems. They found that significant declines in testosterone (and estradiol) are associated with bone loss in men. Despite this finding, the IOM report found insufficient evidence to conclude that fracture risk was higher among hypogonadal aging men. Consistent studies have demonstrated increased lean muscle mass in men receiving testosterone supplementation; however, these studies have not always demonstrated subsequent improvements in muscle strength. Although some evidence exists to support a link between cognitive improvements after testosterone replacement, clinical trials have not consistently demonstrated a benefit. This pattern was also observed for the relationship between mood, depression, and testosterone levels. Some studies have demonstrated benefit, while others have been equivocal. Studies suggest that currently depressed men were more likely to benefit from testosterone replacement. By stimulating erythropoietin production, testosterone replacement increases the red blood cell production (hematocrit) in aging men. Low testosterone levels are significantly associated with hypertension, atherogenic lipid profiles, prothrombotic factors, and type 2 diabetes, all important cardiovascular risk factors. Despite this association with cardiovascular risk factors, no studies have conclusively demonstrated that testosterone replacement alters cardiovascular morbidity or mortality.

Specific aspects of sexual function can improve with testosterone replacement. Most studies support the relationship between libido and testosterone levels. Testosterone replacement has more consistent effects on improving libido than on erectile function. Erectile dysfunction in older men can result from endothelial dysfunction, decreased penile vascular supply (eg, atherosclerotic changes in penile arteries), neurological abnormality (eg, diabetes, surgery for pelvic cancer), or psychological and/or relationship difficulties. Although testosterone can occasionally be an effective treatment for erectile dysfunction in hypogonadal men, specific treatments for erectile dysfunction are available. More recent data suggest that androgen replacement therapy and type 5 selective phosphodiesterase inhibitors (PDEI-5s) may work synergistically to improve erectile function, or that a threshold testosterone level must be achieved for PDEI-5s to work effectively. Recent placebo-controlled, double-blind randomized controlled trial of testosterone versus placebo gel demonstrated increased sexual activity and desire, improved erectile function, improved physical performance, improved mood, and lower severity of depression in the treatment group.

Patient History and Examination

Given the wide range of organs affected by testosterone levels, it is no surprise that hypogonadism is characterized by a variety of nonspecific physical and intellectual alterations. This syndrome is defined by the presence of symptoms or physical findings and the laboratory demonstration of low testosterone to consider treatment for hypogonadism.

A. Symptoms

Adult-onset hypogonadism can result in loss of or a decrease in libido, loss of nocturnal erections, loss of body hair, and reduced muscle strength. A decrease in sexual frequency can often accompany the decrease in sexual desire. Flushing and/or sweating, breast discomfort or gynecomastia, and infertility are also more specific symptoms of testosterone deficiency. Symptoms that are less specific to hypogonadism include fatigue, depression, decline in memory or other cognitive function, increased body fat, diminished work performance, and sleep disturbances.

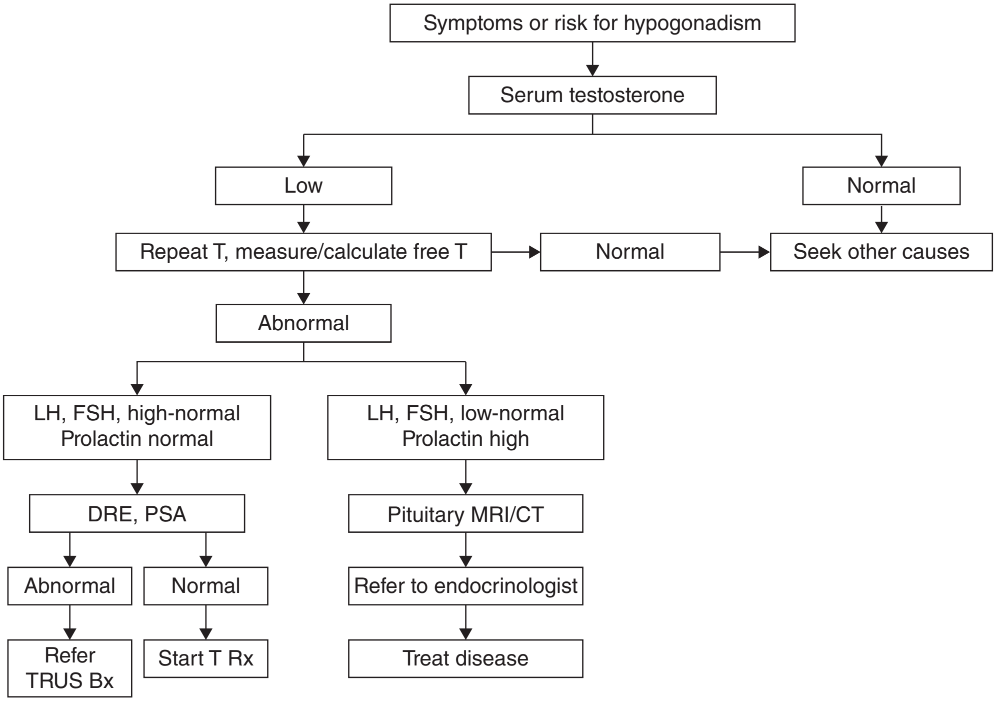
B. Signs

Examination of the man with suspected hypogonadism may reveal breast tenderness or gynecomastia, a decline in lean body mass with associated reduced muscle volume and strength and increase in visceral fat (abdominal girth). Decreased or thinning facial and chest hair and skin alterations such as increases in facial wrinkling and pale-appearing skin suggestive of anemia may also be noted. Anemia tends to be mild and of a normochromic, normocytic type. Low bone mineral density with osteopenia or osteoporosis can also be associated with low circulating testosterone levels. Examination of the genitalia may reveal testicular atrophy with either reduced testis volume or soft consistency.

The diagnosis of hypogonadism does not require all these symptoms and signs to be present. For many men, the natural process of aging, underlying depression or other mood disorders, or other medical comorbidities can be associated with many of these characteristics. Symptoms typical of testosterone deficiency such as decreased mood, impaired cognition, and loss of muscle strength, can all be found in older men despite normal testosterone levels. Despite these observations, the association of such symptoms with repeated low serum testosterone levels implicates hypogonadism as a possible underlying etiology.

Laboratory Findings

There is considerable debate as to what laboratory test should be ordered to diagnose androgen deficiency in aging men. For most men, a fasting total serum testosterone obtained between 7 and 11 am along with a serum SHBG are the two initial tests. A recently published consensus statement supported the lower limit of the normal testosterone in healthy nonobese young men is 264 ng/dL (9.2 nmol/L). Free testosterone can be assessed if there is an altered SHBG or a borderline total testosterone (200–400 ng/dL). For serum testosterone levels less than 150 ng/dL (5.2 nmol/L), serum prolactin should be obtained to evaluate the possibility of a prolactinoma. Values between 230 and 350 ng/dL (8–12 nmol/L) should be confirmed with additional testing with LH, FSH, a repeat serum total testosterone, free testosterone, or calculated free testosterone (using SHBG, serum albumin, and total testosterone; www.issam.ch/freetesto.htm). These confirmatory tests are important to quantify all the non-HBG-bound testosterone. Although reference ranges for bioavailable and free testosterone have been published, these have not been rigorously validated, despite recommendations from the US Endocrine Society to standardize validation methods and a CDC Hormone Standardization Program to help laboratories maintain and enhance results quality. Reference ranges are not age-dependent, as testosterone effects on end organs are the same regardless of a man's age. Free testosterone levels measured by equilibrium dialysis are generally reliable but less widely available than the analog displacement assay. This assay, although widely available, is not a reliable measure of free testosterone. If the measured or calculated active or bioavailable testosterone levels are normal in this situation, then androgen deficiency is unlikely. Low calculated free testosterone levels, even in the presence of normal total testosterone levels, have been associated with more androgen deficiency symptoms, including lower sexual and physical function scores. A working management algorithm for the laboratory diagnosis of androgen deficiency is outlined in Figure 45–5. Currently, the assessment of



▲ **Figure 45–5.** Algorithm for the laboratory diagnosis of androgen deficiency in the male. T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TRUS Bx, transrectal ultrasound and prostate biopsy; MRI, magnetic resonance imaging; CT, computed tomography scan.

levels of testosterone metabolites (eg, DHT, estradiol, and dihydroandrosteindione [DHA]) is not recommended or helpful in the diagnosis of androgen deficiency. An assessment of red blood cell mass with a hemoglobin or hematocrit may be helpful to confirm hypogonadal anemia and is important to establish a baseline prior to the initiation of treatment.

Radiological Testing

As hypogonadism is frequently associated with low bone mineral density and a higher fracture risk, baseline hip and spine bone densitometry should be obtained. Although plain-film x-rays have been used in the past to assess bone mineral density, the DEXA scan is currently the most accurate method. This is an enhanced form of x-ray technology, termed **dual-energy x-ray absorptiometry (DXA or DEXA)**, and is a quick and noninvasive procedure for measuring bone loss. The DEXA machine sends low-dose x-rays with two distinct energy peaks through the body. One peak is absorbed mainly by soft tissue and the other by bone. Soft-tissue absorption is subtracted from the total absorption, resulting in calculated levels of bone absorption that are converted into bone density equivalents. The amount of radiation used is extremely small—less than one-tenth the dose of a standard chest x-ray. Portable devices are also available that measure the wrist, fingers, or heel and are sometimes used for screening. The test is scored in two ways:

1. The *T* score is the amount of bone present compared with a young adult of the same sex with normal bone mass. A score above −1 is considered normal. A score between −1 and −2.5 is classified as osteopenia, the first stage of bone loss. A score below −2.5 is defined as osteoporosis and can be used to estimate the risk of developing a fracture.
2. The *Z* score reflects the amount of bone present compared with others of similar age, size, and sex. Regardless of treatment chosen, bone density assessments should be repeated in 1–2 years to determine whether adequate bone mass is maintained.

TREATMENT OF ANDROGEN DEFICIENCY

Formulations

The primary objective of testosterone replacement treatment for hypogonadism is to restore eugonadal levels of testosterone and ameliorate symptoms and signs of low testosterone, while minimizing the potential for side effects of these treatments. Four major types of hormone replacement are available in the United States: injectable, transdermal, buccal mucosal systems, and pellets (Table 45–5). The most popular formulations are the transdermal gels, injectables,

Table 45–5. Types of testosterone therapy available in the United States.

Available preparation	Formula	Dose	Comments
Parenteral	Testosterone cypionate Testosterone enanthate Testosterone undecanoate	100–400 mg IM q 2–3 weeks 3 mL (750 mg) at baseline; 3 mL (750 mg) at 4 weeks; 3 mL every 10 weeks	Deep IM injection; gives supraphysiologic peaks and low trough hormone levels; mood fluctuations Observe for 30 minutes after administration
Transdermal patch	Testoderm (scrotal) Testoderm TTS Androderm	4–6 mg/day 5 mg/day	Scrotal patch: requires daily shaving, variable absorption Nonscrotal patch: high incidence of skin welts at placement site
Testosterone pellet	Testopel (pellets inserted SQ through 2-mm stab incision in abdomen/superior buttock with local anesthesia)	Available as 75 mg/pellet; initial placement is 8–10 pellets q 3–4 months	Local site infections, extravasation, mood swings, elevated hematocrit
Transdermal gel	AndroGel, Testim, Axiron (applied to clean, dry skin of arm, shoulders, back, thigh, axilla)	2.5–5 mg/day 5 mg/day	Transference of hormone to partner or children; musky odor (Testim)
Clomiphene citrate	Clomiphene citrate 50-mg tablets	12.5–25 mg daily; check T, FSH, LH, E2 3–4 weeks after initiation; adjust dose as needed	Daily oral medication; not always as effective at improving symptoms; does not affect fertility
CG	IM injections	1500 IU 3×/week; check T, FSH, LH, E2 3–4 weeks after initiation; adjust dose as needed	Can be expensive; injections 3×/week can be burdensome; does not affect fertility

pellets, and transdermal patches, in that order. Oral testosterone replacement is associated with an unacceptably high rate of liver toxicity and is not approved for use by the FDA in the United States. More than 95% of prescribed testosterone medication is administered through a transdermal or injectable route. Risks of specific testosterone formulations are summarized in Table 45–5, while general risks are summarized in the next section.

Risks

A. Cardiovascular Disease

The relationship between testosterone and cardiovascular risk is complex. Several population-based studies have demonstrated an association between increased cardiovascular events and testosterone supplementation, without a demonstrated causal relationship. In fact, several studies have demonstrated that higher testosterone levels may decrease the risk of CAD and that low testosterone levels are associated with increased incidence of myocardial infarction and stroke. A large study of 83,000 veterans demonstrated that a normalization of testosterone levels with replacement reduced risk of myocardial infarction, stroke, and all cause mortality. Despite these reassuring findings, the long-term effects of testosterone replacement on cardiovascular functioning are yet to be determined and warrant a thorough discussion between patient and provider.

B. Pulmonary Reactions

Risk of serious pulmonary oil microembolism (POME) reactions (urge to cough, dyspnea, throat tightening, chest pain, dizziness, syncope) and potentially life-threatening anaphylaxis can occur with testosterone undecanoate injection (Aveed). Reactions have occurred during or immediately after administration and may occur at any time during therapy, including after the first dose.

C. Lipid Profiles

Although supraphysiologic doses of testosterone, particularly oral nonaromatizable androgenic steroids, appear to lower HDL levels, numerous studies have demonstrated that physiologic doses of testosterone do not have a significant effect on HDL, total cholesterol, and LDL levels. Testosterone formulation does not appear to alter these relationships.

D. Polycythemia

Evidence suggests that testosterone levels are associated with erythropoiesis. Pubertal boys experience a 15–20% increase in hemoglobin levels in conjunction with increasing testosterone levels. Hypogonadal men often have mild anemia that is improved with testosterone therapy, and testosterone replacement therapy in men with normal hemoglobin levels can result in supraphysiologic hemoglobin levels. The utilization of testosterone injections is most often associated with this side effect.

E. Spermatogenesis and Infertility

Exogenous testosterone of any type generally leads to spermatogenic arrest through negative feedback inhibition of both pituitary LH and FSH secretion. Azoospermia occurs in >90% of patients within 10 weeks. With cessation, sperm levels usually rebound within 18 months, but some patients may remain azoospermic. Patients receiving hormone replacement therapy should be informed that fertility will be impaired on this treatment.

F. Hepatotoxicity

Liver toxicity has been reported with oral administration of methyl testosterone and fluoxymesterone; however, it is only rarely observed with parenteral, transdermal, and transbuccal formulations. Testosterone undecanoate (Aveed) is a testosterone formulation that does not appear to increase hepatic toxicity, although a transient post-injection cough has been reported.

G. Prostate Cancer

Since Huggins first described the relationship between suppression of testosterone levels and regression of prostate cancers in the 1940s, treatments designed to reduce testosterone levels have been used to treat advanced prostate cancer. For many years, the question of increasing the risk of prostate cancer with testosterone supplementation has been unanswered. Early case reports suggested that testosterone therapy unmasked occult prostate cancers. Larger, prospective studies, however, have failed to confirm these anecdotal observations. In fact, the preponderance of evidence suggests that testosterone replacement therapy is not associated with an increased risk of prostate cancer. An observational cohort study of 147,593 Veteran's Affairs patients between 2002 to 2012 with low testosterone tracked intramuscular and topical testosterone replacement therapy did not demonstrate increased incidence of aggressive prostate cancer or prostate cancer overall. Similarly, for men who have undergone successful prostate cancer treatment, testosterone therapy does not appear to increase risk of biochemical recurrence. Despite these reassuring data, proper monitoring with digital rectal examination and serum prostate-specific antigen (PSA) levels are important to diagnose any occult prostate cancers and identify PSA recurrence in prostate cancer patients that may occur after initiating testosterone replacement therapy. Two recent studies, one of 13 testosterone deficient men with untreated prostate cancer on surveillance and another 28 in the treatment arm and 96 without treatment, did not find an association with prostate cancer progression on 30-months and 3-year follow-up, respectively. Given the sparsity of date for men with prostate cancer on active surveillance, the decision to continue or pursue testosterone therapy remains a shared decision made between doctor and patient based on the severity of hypogonadal symptoms and theoretical risks of treatment.

H. Benign Prostatic Hyperplasia

It is known that prostatic enlargement is an androgen-dependent process. Chemical or surgical castration causes a clear decrease in the volume of prostate tissue. Testosterone replacement therapy has been associated with an increase in prostate volume to a level similar to that of eugonadal men. Despite these findings, no changes in urinary flow rate, lower urinary tract symptoms, or postvoid residuals have been noted with testosterone treatment. Furthermore, a higher rate of urinary retention has not been noted with this treatment. However, it is prudent to monitor voiding symptoms as a standard part of routine monitoring.

I. Exacerbation of Sleep Apnea

Testosterone therapy can worsen preexisting sleep apnea. Although not a cause of sleep apnea, testosterone can exacerbate the problem in patients predisposed to the condition (ie, elderly men, obese men, and patients with chronic obstructive pulmonary disease). All potential patients should be questioned for sleep-related breathing disorders before androgen replacement is considered. This side effect appears to be dose-related. A centrally mediated mechanism has been postulated, as no upper airway changes have been noted in men taking testosterone therapy who develop worsening sleep apnea.

J. Fluid and Electrolyte Disturbances

Water retention is known to occur with androgen therapy. In aging men, it can lead to hypertension, peripheral edema, or exacerbation of congestive heart failure. Moreover, retention of sodium, chloride, potassium, calcium, and inorganic phosphates can occur. Weight and blood pressure monitoring are important for at-risk patients.

K. Gynecomastia or Breast Tenderness

Painful breast enlargement due to elevated levels of estrogen (a metabolite of testosterone) frequently develops, and may occasionally persist, in patients on testosterone therapy. Estrogen receptor blockers can be used to treat this side effect.

L. Miscellaneous

Local skin irritation is commonly reported with the use of the testosterone patch. Acne, headaches, emotional lability, insomnia, and hot flushes have been reported with testosterone therapy. The transfer of testosterone to significant others after gel application is minimized by washing the skin site 10 minutes after application. A component of Testim gel, pentadecalactone, has a musky odor that some men find unappealing. Transbuccal formulations (Striant) may cause gingivitis, stinging of the lips, and toothache, and has a bitter taste. Despite these side effects, 60% of men when given the option preferred to continue with a transbuccal treatment approach.

▶ Contraindications and Precautions

Testosterone replacement therapy should not be given to men with prostate cancer, breast cancer, and/or untreated melanoma, as this treatment may increase the growth of these tumors. For men with bladder outlet obstruction related to severe benign prostatic hypertrophy and severe sleep apnea, testosterone replacement therapy should be administered with caution as these symptoms may be exacerbated with this treatment.

At present, there is insufficient evidence to justify the use of testosterone supplementation (not replacement) in men of any age with low–normal but not truly “androgen-deficient” testosterone levels. The IOM consensus statement from 2003 concluded that there was insufficient evidence to justify the use of testosterone therapy for widespread, generalized use for preventing age-related disease or to enhance strength or mood in otherwise healthy older men. The FDA also issued a statement in 2015 cautioning against treatment of low testosterone levels due to aging and requiring all manufacturers of all approved prescription testosterone products to change their labeling to clarify that these medications are approved for use in men with low testosterone levels caused by disorders of the testicles, pituitary gland, or brain.

▶ Monitoring Treatment

Testosterone replacement for hypogonadism is normally a lifelong treatment. Monitoring of the hypogonadal patient should be performed at baseline, at 3–12 months after initiating treatment, and annually thereafter. A digital rectal examination, serum PSA and hematocrit/hemoglobin determination, assessment of voiding function, and sleep apnea assessment are mandatory at the baseline evaluation (Table 45–6). At 3–6 months after treatment is started, the efficacy of treatment and serum testosterone levels should be assessed, along with hematocrit. As testosterone levels can fluctuate, particularly after intramuscular (IM) administration, clinical indicators may be a better guide for adjusting the dose of testosterone. Patients older than 40 years, or those with high risk of prostate cancer, should have a PSA and digital rectal examination 3–12 months after treatment initiation. The history and physical examination at these timepoints should evaluate the presence of gynecomastia, urinary side effects, and changes in degree of sleep apnea. After the first year, patients who remain stable may subsequently be followed annually. Annual evaluations should include testosterone, hemoglobin, liver function tests, lipid profile, and PSA measurements. Bone density and psychological evaluations should be performed depending on the initial indications for androgen supplementation.

Table 45–6. Patient monitoring before and during testosterone treatment.

Time period	Indicated assessment
Baseline (pretreatment)	Hgb, HCT, and PSA level Digital rectal exam Ascertain symptoms of voiding dysfunction and sleep apnea Consider DEXA scan for bone mineral density
1–2 months of treatment	Assess treatment efficacy: testosterone level and symptom relief; consider adjusting dose for either variable
3–6-month intervals during first year	Assess symptomatic response to treatment, voiding symptoms, and sleep apnea Perform physical exam with DRE and obtain testosterone, LFTs, lipid profile, PSA, and Hgb levels
Annually after first year	Assess symptomatic response to treatment, voiding symptoms, and sleep apnea Perform physical exam with DRE and obtain testosterone, LFTs, lipid profile, PSA, and Hgb levels

DEXA = dual-energy x-ray absorptiometry; DRE = digital rectal exam; HCT = hematocrit; Hgb = hemoglobin; LFTs = liver function tests; PSA = prostate-specific antigen.

NONTESTOSTERONE TREATMENTS FOR ANDROGEN DEFICIENCY

5α-Dihydrotestosterone

The natural androgen 5α-DHT is a metabolite of testosterone, resulting from the conversion of testosterone to 5α-DHT by 5-alpha reductase in the scrotum and skin. One of its primary benefits is that it is a very potent androgen, binding to androgen receptors more tightly than testosterone, but it is not converted to estrogen. It is currently available in Europe as a gel application and creates a steady state within 2–3 days of application. Trials have demonstrated improvements in sexual function and lean muscle mass with its use; paradoxically, a decline in prostate volume has been observed after this therapy. This may be so because estrogens may work synergistically with androgens to cause prostatic growth with age and DHT, as a selective androgen, may result in lower estrogen levels during treatment.

Selective Androgen Receptor Modulators

Selective androgen receptor modulators (SARMs) offer a theoretical advantage of tissue specificity. Most of the SARMs in development are nonsteroidal, with the ability to overcome virilizing effects of steroidal androgens. Recent clinical trials have demonstrated increases in lean body mass and improvement in physical function in elderly patients. Animal models have demonstrated promising results in several areas and there are currently SARM phase II clinical trials for breast cancer, stress urinary incontinence, and osteoporosis.

Selective Estrogen Receptor Modulators

Treatment with selective estrogen receptor modulators (SERMs), such as clomiphene citrate (Clomid™) and enclomiphene citrate (Androxal™), have demonstrated significant improvements in hypogonadal symptoms in men with secondary hypogonadism. In one randomized trial, most of the men treated with clomiphene reported improvements in sexual function and gonadotropin levels. A second study demonstrated improvements in serum testosterone levels. Enclomiphene citrate, the isomer of clomiphene citrate, demonstrated effectiveness in maintaining testosterone levels in the normal range while maintaining sperm counts. This treatment can be an effective treatment for hypogonadism in men who desire to preserve fertility. Importantly, since SERMs act by stimulating the hypothalamic–pituitary–gonadal axis, this form of therapy will be effective only among men with sufficient Leydig cell mass to respond to increased secretion of gonadotropins. It is important to note that while these medications have been used off-label for treating male hypogonadism, this is not an FDA approved use of these medications.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) can increase the production of testosterone by binding to Leydig cells and stimulating the release of testosterone. Injections with 1000–2000 IU 2–3 times per week can result in significant increases in serum testosterone levels. For some men, this treatment can also improve spermatogenesis and, as noted for clomiphene citrate, is a good choice for hypogonadal men wishing to preserve fertility.

7α-Methyl-19-nortestosterone

This medication, also known as **MENT**, is 10 times more potent than testosterone, is not bound to SHBG, and is aromatized to estradiol, but does not undergo 5α-reduction to DHT. It has been shown to enhance sexual function with minimal prostatic effect. Lean muscle mass paradoxically declined at high doses with associated increases in prostatic volume.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is available in over-the-counter formulations in the United States and is not regulated by the FDA. DHEA is a steroid hormone made by the adrenal gland and exhibits a progressive decline in serum levels beginning in the third decade of life and beyond. As a consequence of this decline, studies have attempted to correlate levels of DHEA and DHEA sulfate with a myriad of health conditions. Clinical trials that have investigated the DHEA for multiple conditions have shown largely inconsistent findings. Placebo-controlled studies suggest that doses of 30–50 mg of oral DHEA may produce physiologic androgen levels. Clinical trials suggest that 50 mg of oral DHEA, but not <30 mg, can increase serum androgen levels to within the physiologic range for young adults with primary and secondary adrenal insufficiency; improve sexual function, mood, and self-esteem; and decrease fatigue/exhaustion. A recent meta-analysis of DHEA clinical trials in elderly men demonstrated increases in serum DHEA and estradiol levels with supplementation, with no significant increases in total serum testosterone or impact on sexual function and quality of life.

BIBLIOGRAPHY

Epidemiology

Cauley JA et al: Recruitment and screening for the testosterone trials. J Gerontol A Biol Sci Med Sci 2015;70:1105–1111. [PMeaID: 4861649]

Harman SM et al: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86(2):724–731. [PMID: 11158037]

Snyder PJ et al: Effects of testosterone treatment in older men. New Engl J Med 2016;374(7):611–624. [PMID: 26886521]

Changes in Testis Biology with Age

Eskenazi B et al: The association of age and semen quality in healthy men. Hum Reprod 2003;18:447. [PMID: 12571189]

Choi JY et al: Association of paternal age at birth and the risk of breast cancer in offspring: A case control study. BMC Cancer 2005;5:143. [PMID: 16259637]

Ford WCL et al: Increasing paternal age is associated with delayed conception in a large population of fertile couples: Evidence for declining fecundity in older men. Hum Reprod 2000;15:1703. [PMID: 10920089]

Francioli LC et al: Genome-wide patterns and properties of de novo mutations in humans. Nat Genet 2015; 47:822–826. [PMID: 25985141]

Herati AS et al: Age-related alternations in the genetics and genomics of the male germ line. Fertil Steril 2017;107(2):319–323. [PMID 28160920]

Johnson L et al: Quantification of human Sertoli cell population: Its distribution, relation to germ cell numbers and age-related decline. Biol Reprod 1984;31:785. [PMID: 6509142]

Johnson L et al: Age-related variations in seminiferous tubules in men. A stereologic evaluation. J Androl 1986;7:316. [PMID 3771369]

Kaler LW, Neaves WB: Attrition of the human Leydig cell population with advancing age. Anat Rec 1978;92:513. [PMID: 736271]

Kong A et al: Rate of de novo mutations and the importance of father's age to disease risk. Nature 2012;488:471–475.

Lowe X et al: Frequency of XY sperm increases with age in fathers of boys with Klinefelter syndrome. Am J Hum Genet. 2001;69(5): 1046–1054. [PMID 11582569]

Malaspina D et al: Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 2001;58:361. [PMID:11296097]

Martin RH, Rademaker AW: The effect of age on the frequency of sperm chromosomal abnormalities in normal men. Am J Hum Genet 1987;41:484. [PMID: 3631081]

Murray L et al: Association of early life factors and acute lymphoblastic leukaemia in childhood: Historical cohort study. Br J Cancer 2002; 86:356–361. [PMID 11875699]

Practice Committee of American Society for Reproductive Medicine; Practice Committee of Society for Assisted Reproductive Technology: Recommendations for gamete and embryo donation: A committee opinion. Fertil Steril. 2013;99(1):47–62.

Snyder PJ et al: Effects of testosterone treatment in older men. New Engl J Med 2016;374(7):611–624. [PMID: 26886521]

Wang J et al: Genome-wide single-cell analysis of recombination activity and de novo mutation rates in human sperm. Cell 2012;150(2):402–412. [PMID: 22817899]

Yatsenko AN et al: Reproductive genetics and the aging male. J Assist Reprod Genet 2018. (Available online at: https://doi.org/10.1007/s10815-018-1148-y.) [PMID: 29524155]

Yang Q et al: Paternal age and birth defects: how strong is the association? Hum Reprod 2007;22(3):696–701. [PMID 17164268]

Yip BH et al: Parental age and risk of childhood cancers: A population-based cohort study from Sweden. Int J Epidemiol 2006;35:1495–1503. [PMID 17008361]

Diagnosis of Androgen Deficiency

Antonio L et al: Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. J Clin Endocrinol Metab 2016;101(7):2647–2657. [PMID 26909800]

AUA Clinical Guideline Laboratory: Diagnosis of Testosterone Deficiency, 2013. (Available online at: https://www.auanet.org/guidelines/testosterone-deficiency.)

Basaria S et al: Adverse events associated with testosterone administration. New Engl J Med. 2010;363(2):109–122. [PMID 20592293]

Basaria S et al: The safety, pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men. J Gerontol A Biol Sci Med Sci 2013;68:87–95.

Bhasin S et al: Testosterone therapy in men with hypogonadism: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2018. (Available online at: https://doi.org/10.1210/jc.2018-00229.) [PMID 29562364]

Calof OM et al: Adverse events associated with testosterone replacement in middle-aged and older men: A meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 2005;60: 1441. [PMID: 16339333]

Center JR et al: Mortality after all major types of osteoporotic fracture in men and women: An observational study. Lancet 1999;353;878. [PMID: 10093980]

Cheetham TC et al: Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. JAMA Intern Med 2017;177(4):491-499. [PMID 28241244]

Cherrier MM et al: Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: A preliminary report. J Androl 2003;24:568. [PMID: 12826696]

Corona G et al: Dehydroepiandrosterone supplementation in elderly men: A meta-analysis study of placebo-controlled trials. J Clin Endocrinol Metab 2013;98(9):3615–3626. [PMID 23824417]

Dalton JT et al: The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarc Musc 2011;2:153–161

Deutschbein T et al: Total testosterone and calculated estimates for free and bioavailable testosterone: Influence of age and body mass index and establishment of sex-specific reference ranges. Horm Metab Res 2015;47(11):846–854. [PMID: 25565093]

Fisch H: Older men are having children, but the reality of a male biological clock makes this trend worrisome. Geriatrics 2009;64(1):14–17.

Golla V et al: Testosterone therapy on active surveillance and following definitive treatment for prostate cancer. Curr Urol Rep 2017;18(7):49. [PMID 28589395]

Hackett G et al: British society for sexual medicine guidelines on adult testosterone deficiency, with statements for UK practice. J Sex Med 2017;14(12):1504–1523. [PMID 29198507]

Harman SM et al: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724–731. [PMID: 11158037]

Kacker R et al: Can testosterone therapy be offered to men on active surveillance for prostate cancer? Asian J Androl. 206;18(1):16–20. [PMID 26306850]

Kaplan AL et al: Testosterone therapy in men with prostate cancer. Eur Urol 2016;69(5):894–903. [PMID 26719015]

Kim ED et al: Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. BJU Int 2016;117(4):677–685. [PMID 26496621]

Kloner RA et al: Testosterone and cardiovascular disease. J Am Coll Cardiol 2016;67:544. [PMID 26846952]

Kouri EM et al: Changes in lipoprotein-lipid levels in normal men following administration of increasing doses of testosterone cypionate. Clin J Sport Med 1996;6:152. [PMID: 8792044]

Krakowsky Y et al: Initial clinical experience with testosterone undecanoate therapy (AVEED) in men with testosterone deficiency in the united states. Urology 2017;109:27–31. [PMID 28735014]

Morgentaler A et al: Testosterone therapy in men with untreated prostate cancer. J Urol 2011;185:1256–1260. [PMID 21334649]

Mulhall JP et al: Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018 (doi: 10.1016/j.juro.2018.03.115). [PMID 29601923]

Narayanan R et al: Development of selective androgen receptor modulators (SARMs). Mol Cell Endocrinol 2018;465:134–142.

Pfeil E, Dobs AS: Current and future testosterone delivery systems for treatment of the hypogonadal male. Expert Opin Drug Deliv 2008;5(4):471–481.

Rhoden EL, Morgantaler A: Risks of testosterone-replacement therapy and recommendations for monitoring. New Engl J Med 2004;350:482. [PMID: 14749447]

Seftel AD: Male hypogonadism. Part I: Epidemiology of hypogonadism. Int J Impot Res 2006;18(2):115–120.

Seftel A: Male hypogonadism. Part II: Etiology, pathophysiology, and diagnosis. Int J Impot Res 2006;18(3):223–228.

Sharma R et al: Normalization of testosterone levels is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015;36:2706–2715. [PMID 26248567]

Snyder PJ et al: Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 1999;84:1966. [PMID: 10372695]

Snyder PJ et al: Effects of testosterone treatment in older men. New Engl J Med 2016;374(7):611–624. [PMID: 26886521]

Trost LW et al: Challenges in testosterone measurement, data interpretation, and methodological appraisal of interventional trials. J Sex Med 2016;13(7):1029–1046. [PMID 27209182]

Vigen R et al: Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310(17):1829–1836. [PMID 24193080]

Walsh TJ et al: Recent trends in testosterone testing, low testosterone levels, and testosterone treatment among veterans. Andrology 2015;3(2):287–292. [PMID 25684636]

Wang C et al: Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. J Clin Endocrinol Metab 1996;8:3578. [PMID: 8855804]

Wang C et al: Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. J Androl 2009;30:1.

Whitsel EA et al: Intramuscular testosterone esters and plasma lipids in hypogonadal men: A meta-analysis. Am J Med 2001;111:261. [PMID: 11566445]

Winters SJ et al: Laboratory Assessment of Testicular Function, mdtext.com, Inc., South Dartmouth, MA. (Available online at: www.endotext.org; accessed 4/2/18.)

46

Genital Gender-Affirming Surgery: Patient Care, Decision Making, and Surgery Options

Maurice M. Garcia, MD, MAS

INTRODUCTION

Care for the transgender patient is a formally recognized area of focus within the field of urology. Care and surgery of the transgender patient has become a part of this field because of a variety of factors: greater awareness and acceptance of transgender people who live among us, and greater acceptance within medicine of both sexual diversity and gender diversity.

Today we recognize that gender is a spectrum, and not a binary construct. It is highly likely that the urologist of today will see transgender patients in her/his practice. Although genital gender-affirming surgery is emerging as a subspecialty within urology, the general urologist, who may be called on to provide routine urologic care to a transgender patient, or to refer the transgender patient to an appropriately trained urologic reconstructive surgeon, should also be familiar with the care, needs, and surgical anatomy of the transgender patient.

TERMINOLOGY AND CULTURAL SENSITIVITY/INSENSITIVITY

A person's **sex** is assigned at birth and refers to biological factors such as male or female genital/reproductive anatomy, hormone levels, and genes. **Sexual identity** refers to an individual's enduring physical, romantic, and/or emotional attractions to others to define them as heterosexual, homosexual, bisexual, or asexual (Anton, 2009). **Gender** refers to intangible social constructs (behaviors, social roles, attributes, and activities) that a given society considers appropriate to each sex. Gender is defined by society, culture, and social class. **Gender identity** refers to the individual's *own*, complex, and entirely internal sense of self as "male," "female," or "other" on the male–female gender spectrum (APA, 2011). Gender identity is not equivalent to one's sexual orientation. It is useful to consider the difference between gender identity and sexual identity as follows: "Sexual identity is whom one goes to bed *with*, whereas gender identity is who one goes to bed *as*."

A **cis-gender** person is someone whose gender identity conforms to the sex to which that person was assigned at birth within that person's society.

Gender nonconformity refers to the extent to which a person's gender identity, roles, and expressions differ from the norms that a specific society and culture prescribe for the male or female sexes (Coleman et al, 2012). Gender conformity (and nonconformity) are rooted in the dominant societal and cultural norms and are influenced by subculture domains, including socioeconomic status, geography, and history.

Gender nonconformity is not the same as gender dysphoria. Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex (Coleman et al, 2012). **Gender dysphoria** refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and the sex that that person was assigned at birth (Fisk, 1974; Bockting et al, 2011). Not all gender-nonconforming people experience gender dysphoria.

A **transgender** person is someone whose gender identity, gender expression, and behavior do not conform to what is associated with the sex to which that individual was assigned at birth. When referring to someone who is transgender, the prefix **trans-** is coupled with the gender that the individual *identifies with*, and *never* that individual's assigned birth sex. **Gender nonconforming/gender-nonbinary** are terms often adopted by people to better explain or clarify how their gender lies somewhere *in-between* both ends of the spectrum of male-sex/female-sex gender roles. Many individuals do not identify as **transgender**, and prefer the gender-neutral plural pronouns **they** and **them**.

With respect to sexuality, just as with cis-gender people, transgender people can be heterosexual, homosexual, bisexual, or asexual (Coleman et al, 2012).

Gender-related terminology often has different definitions for different people. Terminology also changes over time, and terms used today may either become outdated or change in meaning and nuance. The term **transsexual** has been used more extensively in the body of medical literature related to transgender people, and refers to a person who is transgender and wishes to alter (or already has altered) her/his body by means of hormone supplementation, surgery, and/or other means to render her/his appearance congruent with her/his individual gender identity (APA, 2011). **Transsexual** is an older term, and for some, pathologizing term for transgender people.

Gender identity disorder is now a historical term from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, which explicitly categorizes being transgender as a "mental disorder" and reflects a long history of a pathological view of what it means to be transgender.

In 2012, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, which explicitly categorizes being transgender as a "mental disorder," reflects a long history of changing a common diagnostic term used for transgender people from **gender identity disorder** to **gender dysphoria,** which is defined as the strong and persistent sense of distress caused by a discrepancy between a person's gender identity and birth-assigned sex (Davy, 2015).

Not all transgender people endorse gender dysphoria and, while many are prescribed hormones and surgery to help align their bodies with their gender identity, not all will take these steps (Anton, 2009; APA, 2013).

The term **gender-affirming surgery (GAS)** (Kuzon and Gast, 2016) refers to any surgery performed for the purpose of helping to align a person's body with the gender that she/he identifies with. Other terms for GAS include **gender-confirming surgery** and **sex reassignment surgery**. We prefer GAS because it is more patient-centered. **Gender reassignment** surgery is an older term that today does not make sense, because just as with sexual orientation, gender cannot be assigned, and hence, cannot be *re*assigned.

Culturally Insensitive Terminology

Use of objectifying terms, such as **transgendered**, or using the word **transgender** as a noun, should always be avoided. Even unnecessary use of **transgender-** as a prefix, particularly in casual contexts where a person's gender is immaterial, can be experienced by many as pejorative.

Terms such as **transvestite** and its colloquial variant, "cross-dresser," are often used incorrectly and perceived by gender nonconforming people as pejorative.

When referring to a patient's anatomy or features, use of terms such as "real" or "natural" or other qualifiers that reveal that the speaker does not accept the patient as she/he presents her/himself, can be hurtful, can induce dysphoria, and can undermine a patient's trust in her/his care provider.

Cultural Sensitivity in the Care Environment

Many transgender people change one or all of their birth names either to adopt a name that reflects the gender that they identify with, and/or to rename themselves altogether. Use of each patient's preferred **personal name** and correct **gender pronouns** is important in order to communicate with transgender patients in a way that is culturally sensitive. Indeed, even asking patients for their preferred name, gender, and pronouns can communicate that the provider and care environment are culturally sensitive and welcoming.

When a provider **misgenders** a transgender patient—that is, either addresses that patient by her/his birth name or refers to her/him using pronouns congruent with that person's birth sex instead of the gender that she/he identifies with, doing so can induce significant gender dysphoria. Common manifestations of gender dysphoria described to us by patients include heightened anxiety, depression, insult, resentment, fear for safety, a sense of "not belonging," and a sense of rejection by the provider, which not only harms the patient but also undermines the patient–provider therapeutic bond and relationship.

Being misgendered is one of the most upsetting, and likely most common, negative experiences that a patient can have in the clinical setting. It is also the most easily preventable, as doing so requires only attention to how we address our patients. Effective strategies for all members of the care environment include always remembering to

1. *Ask* patients for their preferred name
2. *Ask* what gender they identify as (man, woman, or gender nonbinary)
3. *Ask* what pronouns they prefer (she/her, he/him, or they/them, respectively)

It is equally important to amend printed intake forms and questionnaires to include the abovementioned domains of gender identity. Asking patients to help the provider and her/his care team serves to convey an *earnest* desire to provide respectful, welcoming care.

Medical Exam-Induced Gender Dysphoria

Medical physical exams can trigger acute and severe gender dysphoria, particularly genital exams, most often pre-genital GAS, but also after surgery. To reduce medical-exam-related dysphoria, it is helpful to, as with any patient, explain the rationale for the exam before commencing, and to use gender-neutral terminology for tissues/anatomy wherever possible. A prostate digital exam can be performed via the vaginal canal (when present).

EPIDEMIOLOGY AND TREATMENT GUIDELINES

Past epidemiological studies of transgender men/women and gender-nonconforming people have been limited by a host of methodological challenges, including selection bias

(Coleman et al, 2012; IoM, 2011). Also, in Western societies gender nonconformity can be less visible for trans-feminine versus trans-masculine individuals. The prevailing view is that the number of transgender people is grossly underestimated in general, especially for trans-masculine and gender-nonbinary individuals.

It's important to note that successively newer studies consistently report increasingly higher incidence and prevalence rates (Arcelus et al, 2015; Zucker et al, 2008, 2012). A statewide Massachusetts study in 2010 found that 1 in 200 people (0.5% of the population) self-identified as being transgender (Conron et al, 2012; NCTE, 2009), and a 2011 study estimated that 0.3% of adults nationwide identified as being transgender (Gates, 2011). The most current US data gathered from a 2016 nationwide study using state-level population-based survey data revealed an effective doubling of the previously estimated number of US adults who identified as transgender to 0.6% (0.7% including adolescents), which is 1.4–1.6 million people) (Flores et al, 2016).

Professional Care and Treatment Guidelines from the World Professional Association for Transgender Health (WPATH)

The **World Professional Association for Transgender Health (WPATH)** is an international professional association of healthcare providers specialized in evidence-based transgender health and gender-affirming surgery, social sciences, and health-rights policy. It publishes the *WPATH Standards of Care Guidelines* (AMA, 2008). Although originally presented only as care guidelines for use the world over, these are now endorsed by many leading medical professional organizations, including the US Department of Health and Human Services, and are referred to by the majority of US health insurance companies.

Gender dysphoria *can* in large part be alleviated through treatment (Murad et al, 2010). Greater public visibility and awareness of gender diversity (Feinberg, 1996) has further expanded options for people with gender dysphoria to actualize an identity and find a gender role and expression that are comfortable for them. Treatment for gender dysphoria has become more individualized; the therapeutic approaches that help alleviate gender dysphoria for one person may be very different from what helps another person.

A variety of therapeutic options are now available to individuals with gender dysphoria to achieve comfort with self and identity and to find a gender role and expression that are comfortable for them, even if these differ from those associated with their sex assigned at birth, or from prevailing gender norms and expectations.

It is important to recognize that the number, type, and order of these interventions *will* vary from person to person, and, by some transgender and gender-nonconforming people with or without gender dysphoria may choose to undergo *no* intervention at all (Bockting et al, 2006; Bolin, 1996; Garcia et al, 2017; Rachlin et al, 2008, 2010). Being transsexual, transgender, or gender-nonconforming is a matter of diversity, not pathology (Coleman et al, 2012).

Treatment options include the following:

1. Psychotherapy/counseling (individual, couple, or family) for a variety of purposes: (a) helping individuals explore their own gender identities, expressions, and roles; (b) management of the negative effect of gender dysphoria on mental health; (c) alleviating internalized (or environmental) transphobia; (d) enhancing social support; and (e) discussion of gender transition-related options.
2. Enacting part- or full-time changes in gender expression and role, consistent with the individual's own gender identity.
3. Social and gender expression support services: in-person and online peer support services, counseling to improve verbal and nonverbal communication in alignment with the identified with gender, hair removal, and legal name and gender designation change.
4. Cross-sex feminizing (estrogen-based) or masculinizing (testosterone-based) hormone therapy. Feminizing hormone therapy often also includes an oral antiandrogen (eg, spironolactone) and in some cases, also progesterone (for feminizing fat distribution). Masculinizing hormone therapy may include finasteride to prevent testosterone-related hair loss).
5. Surgery to change primary or secondary sex characteristics to align the body with the identified-with gender (see section on surgery below).

Today we recognize that while many individuals need the combination of psychotherapy together with hormone therapy and gender-affirming surgery to alleviate their gender dysphoria, others need treatments from a combination of only some of these domains (Bockting et al, 2006; WPATH, 2011; Lev, 2004; Bockting, 2008).

Gender-Affirming Surgery

A wide spectrum of gender-affirming surgeries (GASs) (Kuzon and Gast, 2016) exists for patients (Table 46–1). Surgery, particularly genital surgery, is often the last and most

Table 46–1. Gender affirming surgeries: overview.

Feminizing	Masculinizing
Facial feminization	Masculinizing facial surgery
Thyroid-cartilage reduction	Bilateral mastectomy
Vocal cord surgery	Masculinizing genital surgery
Breast augmentation	
Body contouring (with filling agents)	
Feminizing genital surgeries	

widely considered part of the process of gender transition. For many individuals, body-modifying surgery is essential and medically necessary (Hage and Karim, 2000). Surgery can help people feel more comfortable and confident in certain romantic, social, and public environments. Surgery may also reduce harm in the event of arrest or incarceration. Recent studies have consistently shown unequivocal benefit to patients in the domains of well-being and mental health, cosmesis, sexual function, and social adjustment (Rachlin et al, 2017; De Cuypere et al, 2005; Gijs and Brewaeys, 2007; Klein and Gorzalka, 2009; Pfafflin and Junge, 1991).

Criteria for Breast/Chest and Genital Gender-Affirming Surgeries

The WPATH SOC guidelines recommend that a list of criteria (Table 46–2) be met for all breast/chest and genital surgeries. This list includes the requirement that persistent gender dysphoria be present and documented by a qualified **mental health professional**. The types of surgery, and their sequence, should be based on an individualized assessment of clinical need.

Surgery Referral Letters

Gender-affirming surgeries of the chest/breast and genitals are performed for the treatment of gender dysphoria, and not routine elective, or merely "aesthetic" procedures. Rather, they are performed specifically for the treatment of a medical diagnosis of **gender dysphoria** (ICD-10 F64.1). As such, these surgeries should be performed only after assessment by one or two qualified mental health professionals. As outlined in Section VII of the WPATH SOC (version 7.0), a surgery referral letter should comment on (1) whether the patient meets guideline criteria to proceed with surgery, (2) the patient's insight/understanding about and capacity to consent for the surgery that she/he is scheduled to undergo, and (3) whether there are any limitations to resources and support that might adversely affect the her/him during recovery. The surgeon should *also* consider all of these points independently and communicate directly with the referring mental health provider(s) should any concerns about the patient's fitness for surgery arise. By following this recommended approach, mental health professionals, surgeons, and the patient *share* in the discussion and decision to proceed with these irreversible surgical procedures.

Table 46–2. Criteria for gender affirming surgery (Coleman, E, 2012).

Criteria	Surgery*
1. Persistent, well-documented gender dysphoria 2. Capacity to make a fully informed decision and to consent to treatment 3. Age of majority 4. If significant medical or mental health concerns are present, these must be well controlled 5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones not clinically indicated) 6. 12 continuous months of living in a gender role that is congruent with the patient's gender identity	A. Mastectomy/creation of a male chest for MtF patients: # 1–4, *left;* Breast augmentation (implants/lipofilling) for FtM patients: # 1–4; #5 is *recommended* (but not an explicit criterion) to maximize pre-op breast growth/improve outcomes B. Hysterectomy/oopherectomy for FtM patients, and bilateral orchiectomy for MtF patients: #1–5, *left* (criteria do not apply if surgery for medical reasons *other than* gender dysphoria C. Metoidioplasty or phalloplasty for FtM patients, and vaginoplasty for MtF patients: #1–6, *left. Recommended* (but not an explicit criterion): regular visits with a mental health or medical professional

*Surgery referral letters by qualified mental health professionals are required: one for A, two for B & C.

Genital Gender-Affirming Surgery

Three equally important aspects of genital GAS are (1) elimination or removal from view of birth-sex genitalia, (2) creation of genitalia whose appearance aligns with the gender the patient identifies with; and (3) genitalia whose function is in alignment with the gender they identify with. For **transgender** individuals seeking genital GAS, the genitalia sought are commonly, although not always, those of the opposite sex. A transgender man may, for example, elect to undergo several male gender-affirming surgeries, including phalloplasty, yet he may choose to preserve his vaginal vault for sexual function. Individuals whose gender identity is **nonbinary**, similarly, may seek only some components of genital GAS, and not others (eg, hysterectomy, vaginectomy and metoidioplasty with urethral lengthening, but not scrotoplasty with testicular prosthesis placement). Ultimately, gender-affirming surgery—like gender—is a **spectrum**.

Although the spectrum of genital GAS is outlined and discussed below as being divided among **male-to-female** (MtF) and **female-to-male** (FtM) surgeries only for simplicity of presentation, we recognize that patients may elect to undergo only some of the component surgeries.

Genital gender-affirming surgery (Kuzon and Gast, 2016) provides patients with genitals that appear and function as much as possible as the genitals of the sex with which they identify. In our experience, for most patients, it is equally (if not often more) important that surgery *eliminate* any visibility of the sex they were assigned at birth as it is that surgery *create* genitalia of the sex and gender that they identify with.

A. Feminizing (Male-to-Female [MtF]) Genital GAS

Feminizing genital GAS serves patients in three important ways: (1) to eliminate dysphoria-inducing male-appearing genital anatomy, (2) to eliminate the source to masculinizing testosterone (ie, the testes), and (3) to create genital anatomy that is female in both appearance and function.

Testosterone secreted by the testicles has effects that counter a transgender woman's gender transition; it maintains undesired masculine secondary sex characteristics, and diminishes the desired feminizing effects of cross-sex hormone therapy (ie, exogenous estrogens, antiandrogens, and other hormones that many patients take). Also, by providing a "male" hormonal milieu for the brain, it likely exacerbates gender dysphoria in ways that we are still only beginning to understand. **Bilateral orchiectomy** can be performed by itself, as a standalone procedure, or, more commonly, as part of the more complete genital GAS surgery commonly termed **vaginoplasty**, wherein all male-appearing genital anatomy is removed and/or reconstructed to create genitals that mirror those of a cis-gender female.

Feminizing genital GAS can be divided into the following procedures:

1. Bilateral transscrotal orchiectomy (as a standalone procedure)
2. Complete vaginoplasty without creation of a vaginal canal
3. Complete vaginoplasty with creation of a vaginal canal by one of four options:
    a. Vaginal canal created by penile inversion alone
    b. Vaginal canal created by penile inversion augmented with free full-thickness scrotal skin grafts
    c. Vaginal canal created by penile inversion augmented with scrotal skin as a pedicle flap
    d. Vaginal canal created exclusively by an intact segment of colon

B. Bilateral Orchiectomy

Gender-affirming bilateral orchiectomy—performed either (1) as a standalone procedure for patients who elect to undergo orchiectomy but do not plan to undergo vaginoplasty or (2) *before* vaginoplasty when there is a minimum of ~ 4 months; wait before vaginoplasty can be performed—has several potential advantages for any patient (Table 46–3).

Bilateral orchiectomy should be performed using a transscrotal approach via a single vertical-midline incision.

Table 46–3. Potential benefits of bilateral orchiectomy as a stand-alone procedure for the transgender patient.

1. Discontinue use of an androgen-blocking agents (eg, Spironolactone, a potent diuretic) and eliminate their negative side effects
2. Decrease estrogen dosage, typically by 50% (→ reduces negative effects of estrogen on the cardiovascular system; reduces the increased risk of DVT associated with estrogen use, especially among smokers)
3. Eliminates the masculinizing effects of testosterone on secondary sex characteristics (eg, facial hair, skin)
4. Facilitates *tucking* (reducing the visibility of the penis through clothing by tucking it far posteriorly, between the legs) and eliminates testicular pain associated with tucking
5. Many patients describe to us that for them it reduces the "male appearance" of the genital area, which helps decrease overall gender dysphoria
6. Many patients describe to us a noticeable decrease in their gender dysphoria once their systemic testosterone levels decrease (mental health benefits akin to the known positive effects of systemic female hormones?)

C. Vaginoplasty

With **vaginoplasty** surgery, a female vulva (the medical term for the external female genitalia) is created by a combination of removing male structures (testes, penile shaft and penile urethra, a majority of the glans penis, and nearly all of the scrotum), and reconstructing the residual genital tissues to create the key structures of a vulva and vagina.

Vaginoplasty surgery can be offered either *with* creation of a vaginal canal, to afford receptive vaginal intercourse (referred to as **full-depth vaginoplasty**) or, it can be offered *without* a vaginal canal—which *we* term **shallow-depth vaginoplasty** (sometimes also referred to as **zero-depth vaginoplasty**, or vaginoplasty without canal, and **vulvoplasty**). When reviewing surgery options with a patient, both full-depth and shallow-depth options should be reviewed, as each is associated with relative advantages and disadvantages.

1. **Review of vaginoplasty surgical options**—We emphasize to patients that the *only* anatomic difference between the full-depth and shallow-depth options is the presence or absence of a vaginal canal, respectively. Our discussion about these two surgical options *always* includes the essential discussion points listed below. The product of vaginoplasty *with* creation of a vaginal canal is visibly identical to the product of vaginoplasty *without* creation of a vaginal canal; both are indistinguishable by visual inspection.
    - Choice to undergo creation of a vaginal canal absolutely requires that the patient commit to regular and lifelong vaginal dilation and douching in order to maintain patency and hygiene of the vaginal canal.
    - Failure to adhere to a strict dilation regimen places the patient at significant risk of stenosis of the vaginal canal, which *will* result in loss of depth and width of the canal, compromising or eliminating its usability for intercourse. Stenosis may also result in failure to drain natural waste (skin turnover, sweat, oils) from the skin lining the canal, which can result in infection, pain, and foul odor.
    - Erogenous sensation capable of resulting in orgasm is derived reliably from the neoclitoris and the clitoral area, which are created during vaginoplasty, regardless of whether one chooses to undergo creation of a vaginal canal.

    We review our recommended vaginal dilation schedule for a vaginal canal made from penile skin and/or scrotal skin (each dilation is 20 minutes); tid (3 times daily) for the first 3 months postoperatively, then bid (twice daily) for months 4–18, qd (once daily) for months 19–36, and then 3–4 times per week thereafter. We explain that there are no reliable data to indicate how many years after surgery a patient needs to dilate for, and that hence, the patient should be prepared to continue dilating for the rest of their life until outcome studies suggest otherwise.

2. **Communication and management of expectations—** Patients should consider which vaginoplasty option best suits their needs regarding their unique sexual preferences, practical needs, and personal preference. For example, patients for whom vaginal receptive intercourse is an integral aspect of satisfactory sexual function might reasonably require creation of a vaginal canal. For other patients, the ability to be able to forego the need to self-dilate and douche their vaginal canal on an ongoing basis may outweigh any potential benefits of a canal. Examples include patients (a) for whom vaginal receptive intercourse is unimportant or only minimally important, (b) who do not anticipate being sexually active after surgery, and (c) who are sufficiently self-aware to know that (for whatever reasons) they are unlikely to be able to adhere regularly and reliably to dilation and douching.

Some patients may have difficulties either from harboring unreasonable expectations as to what they believe is "correct" for how a vagina should look or what specific anatomic features a vagina should have. We have developed a discussion and teaching aid that uses cast images of cis-gender women's vaginas across various age groups, to advance what we consider to be three key insights that some patients may need help accepting: (a) all vaginas are different, and there is no gold standard for appearance; (b) because the patient's genital area tissue is limited in quantity and type, it is not feasible to create particular anatomic features, such as exaggerated labia—we explain that because anatomy is a spectrum (and we refer to the image of the casts shown), patients can expect truly normal labial anatomy (for example), but of the sort that has less rather than more prominent labia; and (c) some women are strongly biased in the belief that only a vagina with a canal is "real," and that one without a canal is a compromise—regardless of whether they plan to use the canal. While we always respect patient's views, many find it helpful to consider a canal considering the following points made with option (c), namely, that the vaginal canal in any woman's vagina is never visible (ie, one cannot look into a vagina). Yet, looking at the images of the casts, what we see is unequivocally a "vagina." It follows from this that a **vaginal canal**, or degree of **vaginal depth**, does do not define whether what is visible is or is not a vagina. Rather, it is what is visible that defines whether we call it a vagina, and, vaginas with and without a canal are indistinguishable.

Examples of patient characteristics that *may* make them *unsuitable* candidates for creation of a vaginal canal include patients (1) with physical limitations (eg, lack of sufficient manual dexterity, vision, and/or sufficient mobility of their back or neck to reach down to their genital area to dilate and douche) and (2) who do not have a reliable and safe place to regularly dilate and douche (eg, being homeless, being frequently incarcerated, or otherwise living in environments without access to dilators or douche kits).

Terminology related to female genital structures can be confusing and controversial. By strict medical definition, the **vulva** is the portion of the female genitals that is external and hence visible, whereas **vagina** refers to the vaginal canal, which is out of view and connects the vulva to the uterus. In our experience, *non*medical (lay) transgender and cisgender people, however, who represent the vast majority of our patients, generally use the term **vagina**, instead of **vulva**, to refer to a woman's genital area visible externally. Regarding gender-affirming care, we feel that the terminology for anatomy (vagina) and surgery to create female genitalia (vaginoplasty) should be *patient-centered* and respectful, much in the same way that we have learned that transgender patients consistently feel acknowledged and respected when we invite them to provide their preferred name and gender in the clinical setting. Use of terminology that is foreign to people (or worse, that they do not understand), and which, by being different from commonly used terms, can make female patients feel different from other women, risks being stigmatizing and invalidating to patients, and undermines an effective patient–provider relationship. For these reasons we *prefer* to use the term **vagina** for the female genitals that we create with GAS and **vaginoplasty** for the surgical procedure regardless of whether the surgery includes creation of a vaginal canal. We have found that, among our patients, the term **shallow-depth vaginoplasty** is preferred over "zero-depth vaginoplasty," "vaginoplasty without canal," and "vulvoplasty." Provided that the discussion about the key differences between surgical options is thorough and completely clear to patients, using less potentially stigmatizing terminology, whenever possible, is beneficial.

SURGICAL ANATOMY

The principal components of a vulva (clitoral shaft, **glans clitoris**, clitoral hood, appropriately shortened urethra, **labia minora**, **labia majora**, and vaginal introitus, are all created using local tissues harvested from local native male structures immediately before the male structures are resected. Table 46–4 shows the native male structures (*left column*) that are reconstructed to create the principal components of the neovagina (*right column*) and the female homologs to the native male structures (NCTE, 2009).

It is beyond the scope of this chapter to present detailed surgical technique (and more than one vaginoplasty technique can be used). Nonetheless, we outline here the principal structures of the female vulva and vagina and explain what male anatomic structures are utilized to create the homologous female structures.

Table 46–4. Gender-affirming vaginoplasty surgery.

Native male structure	Native female homolog	Neovaginal structure
Bulbar urethra	(urethra)	1. Pink back-wall of vulva between clitoris and urethral meatus; 2. Neovaginal urethral meatus
Penis shaft (Corpora cavernosa)	Clitoral shaft (corpora of clitoris)	Clitoral shaft (onto which neoclitoris is secured)
Glans penis (anterior aspect)	*Glans clitoris*	Neoclitoris
Distal penile shaft skin (1 cm in continuity with anterior glans penis)	*Clitoral prepuce (skin hood)*	Neoclitoral prepuce (skin hood)
Penis dorsal neurovascular bundles (NVB)	Clitoris dorsal NVB	Neoclitoris dorsal NVB
(With full-depth vaginoplasty only): Penile shaft skin (shaft base to 1 cm proximal to coronal ridge of glans penis)	Clitoral shaft skin	Lining of neovaginal canal
(With full-depth vaginoplasty only): Suprapubic skin (midline skin immediately cephalad to base of penis shaft)		Neo-Labia minora
Penile shaft skin *with zero-depth vaginoplasty* (shaft base to 1 cm proximal to coronal ridge of glans penis)	Clitoral shaft skin	Neo-Labia minora and blind-ending vaginal introitus (skin-dimple)
Penis shaft skin surrounding shaft-base	Anterior and posterior vaginal commissure	Anterior and posterior neovaginal commissure
Median raphae	Labia minora	
Scrotal skin	Labia majora skin	Medial aspect of neo-Labia majora (lateral aspect is composed of groin skin lateral to scrotum)

In Table 46–5, we review the surgical steps for any vaginoplasty, adding description later in this chapter about how to create the vaginal canal and line it with epithelium harvested from one or more of the various donor sites available (Table 46–6): penis skin alone, penis skin augmented with scrotal skin, or a pedicled segment of right colon. A common aspect of surgery types 1–4 listed in Table 46–6 is that in types 1–3 the penile skin is used to fashion the vaginal opening, resulting in types 1–3 all appearing the same externally. Only type 4 (colon vaginoplasty) incorporates an epithelium other than skin to create the vaginal opening (ie, colon mucosa).

We generally construct genital anatomy with proportions similar in size and shape as cis-gender anatomy. Nonetheless, some patients may request that parts of their new anatomy be more or less pronounced; when possible, such requests are accommodated.

Initial Dissection: Perineal Incision

We perform vaginoplasty via a midline incision through the perineum and scrotum.

After the perineal incision has been made Figure 46–1, key male genitourinary anatomic structures come into view and serve as the substrate from which female genitourinary anatomy is created (Figure 46–1).

Dissection of the Vaginal Canal Space

The **vaginal canal space** is created by careful dissection through the **perineal body** (also known as the **central tendon**), and along the natural avascular tissue plane located anterior to **Denonvillier's fascia**, and posterior to the prostate and bladder (Figure 46–2).

This dissection of carried out by rotating the prostate anteriorly and making a horizontal incision through the insertion of DVF onto the posterior aspect of the prostate apex.

Shallow-Depth Vaginoplasty Technique

When vaginoplasty is performed without creation of a vaginal canal (ie, **shallow-depth vaginoplasty**), because there is no need to create the vaginal canal space, the penile skin is detubularized by incising it at ventral midline, and the distal penile skin is instead sutured to the posterior end of the perineal incision, to create the posterior commissure. Just anterior to the posterior commissure, this skin is gathered to create a "dimple" of skin identical in appearance to the dimpled skin visible at the vaginal introitus when a canal *is* present.

Table 46–5. Vaginoplasty surgical anatomy and general steps.

1. Vertical perineal Incision
2. Dissection of the urethral bulb;
3. Rotation of prostate, with Incision of perineal body and terminus of DVF*
4. Dissection of vaginal canal space*
5. Degloving of penis from penile skin
6. Dissection of neurovascular bundle and creation of neoclitoris
7. Transection of proximal penile urethra; proximal dissection to confluence of penile crura
8. Penectomy
9. Ventral spatulation of proximal urethral segment; creation of urethral introitus
10. Vertical midline "window" through anterior penile skin for urethra and neoclitoris to pass through
11. Placement of penile skin tube into vaginal canal with creation of vaginal introitus posterior commissure *OR* suturing of distal penile skin to posterior end of perineal incision to create posterior commissure
12. Excision of redundant scrotal skin; creation of Labia Majora/ Labia Minora
13. Creation of clitoral hood

Degloving the Penis and Construction of the Neoclitoris

The penile shaft skin is separated from the penis by dissecting along the natural surgical plane between Buck's fascia (deep) and Colle's fascia (superficial).

A sensate ***neo*clitoris** is created by preserving the proximal dorsal portion of the glans penis together with the dorsal neurovascular bundle (NVB) of the penile shaft**.**

A **clitoral hood** is made for the neoclitoris using a 1-cm cuff of penile shaft skin that is left intact with the glans tissue harvested to create the neoclitoris; the left and right edges of this cuff of skin are sewn to each other at midline to create the inner aspect of the clitoral hood (Figure 46–3).

After the NVB and glans tissue that will become the neoclitoris are dissected free from the penile shaft, **penectomy** is performed by transecting the penile shaft at its base (approximately 1 cm distal to where the two penile crura join to become the penile shaft), and oversewing the left and right tunica edges of the shaft both for hemostasis and to create a flat surface (Figure 46–3B, right; Figure 46–4A, green outline). In this way, the oversewn penile shaft stump serves as the **neoclitoral shaft**, and the neoclitoris is sutured at midline to its anterior aspect. The **redundant length of NVB** is folded secured at midline to fascia cephalad to the clitoris with a fine PDS suture placed through NVB-investing fascia (Figure 46–3B, right). This segment of NVB is highly sensitive and for most patients is capable of producing an erogenous sensation and orgasm of the same quality as that produced by the neoclitoris, but without the hypersensitivity from the neoclitoris that most women report experiencing (Garcia, 2018). Note that the newly fashioned neoclitoral shaft always has a fixed location: at the confluence of the penile crura, abutting the inferior aspect of the pubic symphysis). The native urethra is placed to gentle traction and is transected at the point where it overlaps with the neoclitoris.

Table 46–6. Surgical techniques and tissue donor-site options to line the vaginal canal space.

1. Penile inversion (penile shaft skin; pedicled flap)
2. Penile inversion augmented with scrotal-skin grafts (free full-thickness scrotal skin grafts)
3. Detubularized penile skin augmented with a scrotal-skin flap (posterior scrotal skin pedicle flap)
4. Colon vaginoplasty (intact, pedicled segment of right ascending or sigmoid colon)

Creation of the Urethral Neointroitus and the External Features of the Vagina

The resulting urethral stump (Figure 46–4A, blue arrow) is placed into mild traction, is marked where it reaches the neoclitoris, and is transected with scissors (Figure 46–4B, blue dotted line).

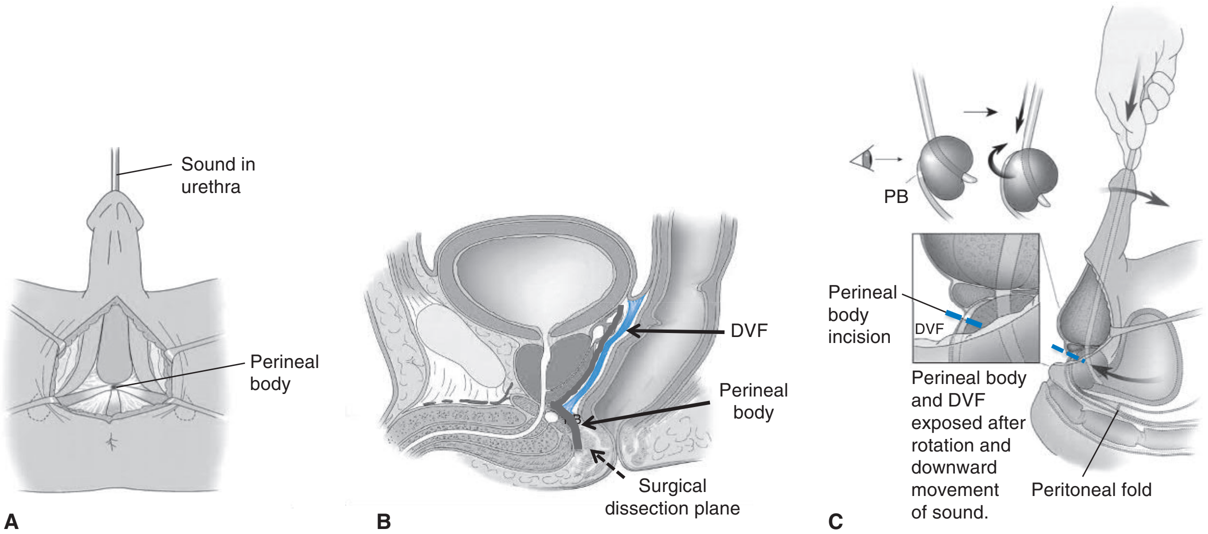
The ventral midline aspect of the urethral stump is then detubularized distal to proximal (Figure 46–4C), leaving the urethra (proximal bulbar) intact where it courses due **cranial–caudal** (ie, at the point where the urethral lumen changes course from being directed anteriorly to being directed downward when the patient is in a sitting position). This location on the (still tubular) urethra will be the location of the new **urethral introitus** (Figure 46–4D, blue arrow**)**. It is important that the new urethral introitus be located where the urethra is caudally oriented because if the lumen of the urethra is oriented anteriorly, the urinary stream will not direct downward into a toilet when the patient voids in a sitting position, and patients often complain that they wet their inner thighs with urine when voiding while seated. Insertion of an "olive tip" (**Bougies-a-Boule**) urethral sound in the urethral introitus during this dissection helps to confirm the location and trajectory of the urethral lumen.

Furthermore, during placement of an indwelling urinary catheter in someone with this anatomy, the catheter will be passed in a caudal–cranial orientation.

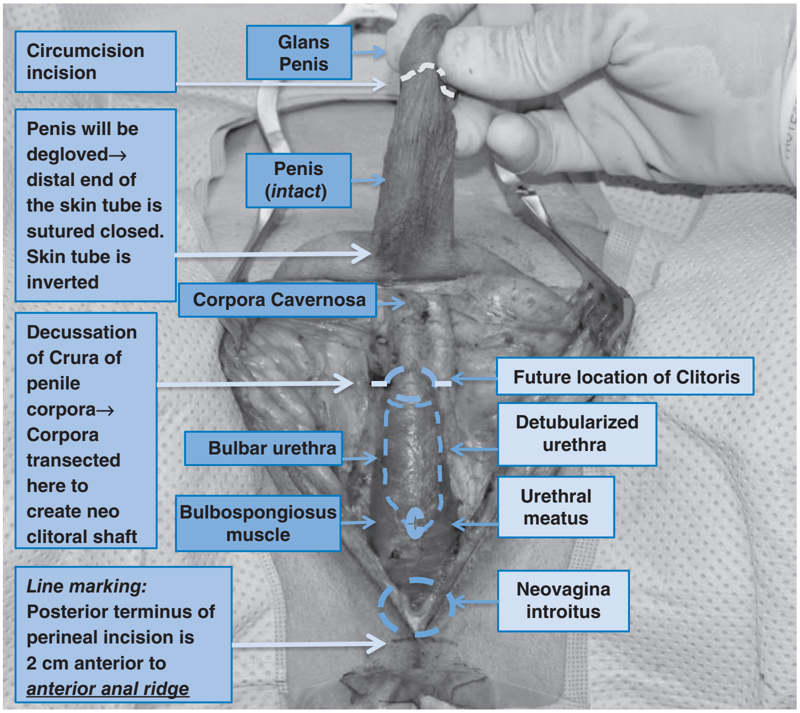
The mucosa of the detubularized urethra is then oversewn along to the fascia of the urethral bulb along the perimeter of the urethra (Figure 46–4D, green line).

All cis-gender women's vulvas, regardless of the individual's skin color, have a pink-colored posterior wall. To achieve similar anatomy with vaginoplasty, the stump of penile/bulbar urethra is detubularized to expose its pink mucosal lining (Figure 46–4D, green line).

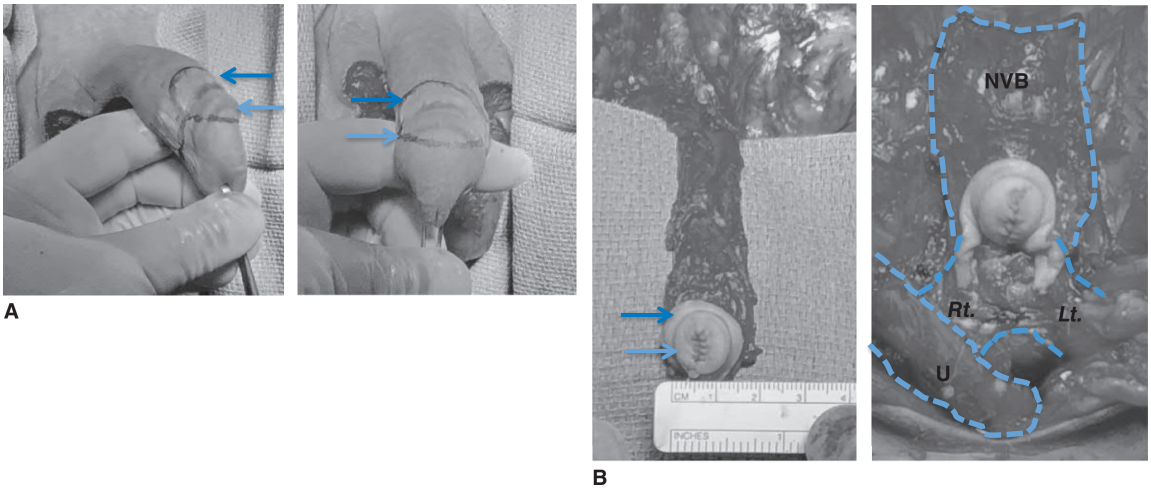
When the penile skin tube is inverted and inserted into the vaginal canal space, its base is pulled posteriorly (to


Sound in urethra
Perineal body
A
DVF
Perineal body
Surgical dissection plane
B
PB
Perineal body incision
DVF
Perineal body and DVF exposed after rotation and downward movement of sound.
Peritoneal fold
C

▲ **Figure 46–1.** ***A:*** The perineal body (or *central tendon*) anchors the base of the bulb of the urethra to the transverse peroneus muscles and to the coccyx. ***B:*** Denonvillier's Fascia (DVF) (*blue*) is a reflection of peritoneum at the rectovesical peritoneal pouch that terminates at the perineal body. It extends between and separates the prostate and bladder *anteriorly* from the rectum *posteriorly*. The surgical plane *anterior* to DVF is relatively avascular. ***C:*** The neovaginal canal space is created *anterior* to DVF and *posterior* to the bulb of the urethra, prostate, and bladder *anterior* to DVF.


Circumcision incision
Glans Penis
Penis will be degloved→ distal end of the skin tube is sutured closed. Skin tube is inverted
Penis (intact)
Corpora Cavernosa
Decussation of Crura of penile corpora→ Corpora transected here to create neo clitoral shaft
Future location of Clitoris
Bulbar urethra
Detubularized urethra
Bulbospongiosus muscle
Urethral meatus
Line marking: Posterior terminus of perineal incision is 2 cm anterior to anterior anal ridge
Neovagina introitus

▲ **Figure 46–2.** Vaginoplasty midline perineal dissection. *Medium-Blue*: Key incisions and surgical steps. *Dark-Blue*: Natal male structures encountered during the dissection. *Blue*: Location of corollary female structures created during vaginoplasty



▲ **Figure 46–3.** ***A:*** A small section of the glans penis (*dark-blue arrows*), centered at midline and incorporating the glans coronal ridge is incised and preserved, together and contiguous with a 1 cm cuff of distal penile shaft skin (*light-blue arrows*), which will serve as inner-lining of the clitoral hood. ***B:*** (*Left*) The Neurovascular bundle (NVB) has been dissected off of the corpora, and wedge-shaped segment of glans tissue harvested from the glans (*light-blue arrow*) has been sutured together at midline to create the neo clitoris glans. (*Right*) The clitoris has been sutured into place at midline over the oversewn stump of the penectomy site (confluence of the Lt. and Rt. corpora cavernosa). The redundant length of NVB is secured to suprapubic fascia (NVB), and is a source of erogenous sensation. The stump of bulbar urethra (U) will be further shortened and will be secured to the posterior edge of the clitoris.

reside posterior to the base of the urethral bulb), where it will serve as the vaginal canal introitus. Doing so causes skin from the anterior aspect of the penile skin shaft to obscure all midline tissue located between the clitoris and the new urethral introitus. In order to create an opening through which the new clitoris and urethral introitus can be externalized, a vertical midline incision is made in this anterior penile shaft skin (Figure 46–4E, F). The length of this incision is approximately equal to the distance between the neoclitoris (anteriorly) and the new urethral meatus (posteriorly) (Figure 46–4E–G).

The edges of the detubularized urethra (Figure 46–4D, green outline) are then sutured to the ipsilateral skin edges of the vertical midline incision made through the anterior aspect of the penile skin tube (Figure 46–4F, left/right-side arrows). The result is shown in Figure 46–4H**.** Note that the skin over the clitoris is sutured together at midline to form the anterior wall of the clitoral hood. A urethral catheter is shown in place.

Labia minora are fashioned from folds along the penile shaft skin on either side of midline between the clitoris and the posterior aspect of the vaginal canal introitus. **Labia majora** are created by first excising the prominent flap of redundant scrotal skin that results when the vaginal introitus is made by suturing together skin from the posterior edge of the base of the penis to the posterior end of the perineal incision (ie, the posterior commissure). The resulting skin edges lateral and medial to where the scrotal skin is resected are sutured together, to create the labia majora.

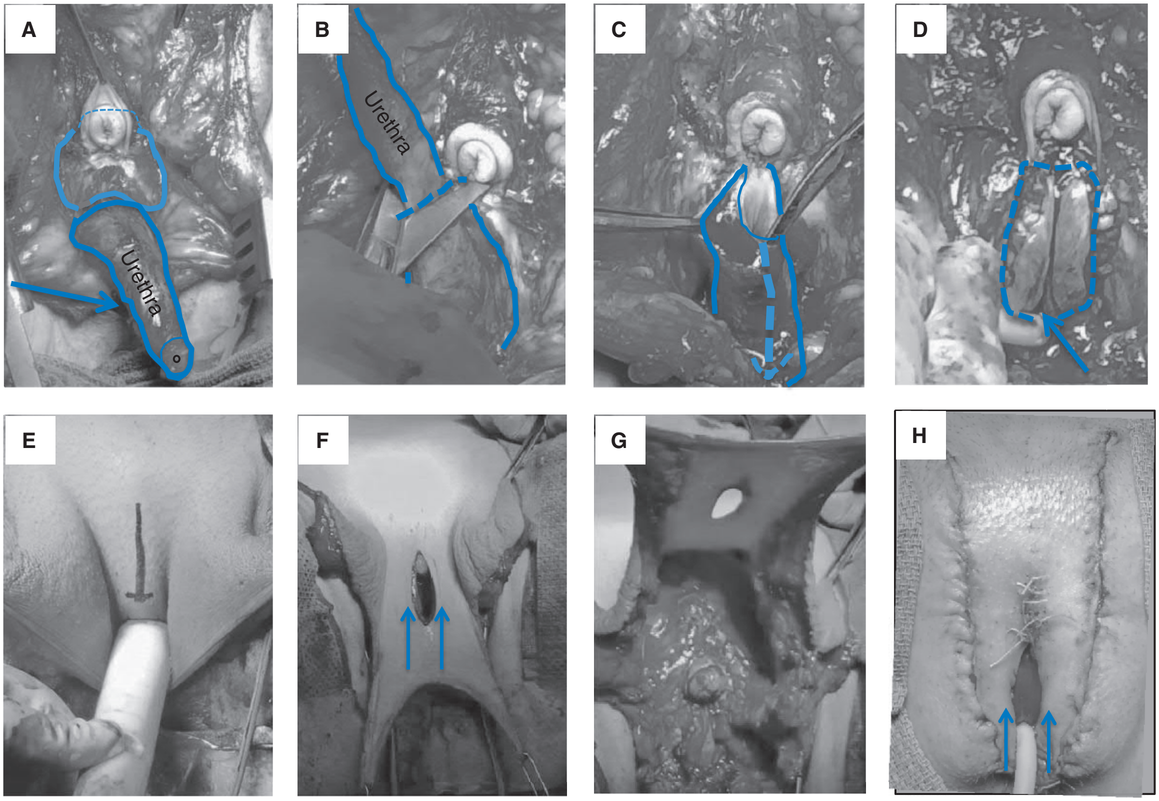
OTHER GENDER-AFFIRMING SURGIAL OPTIONS, COMPLICATIONS, AND TECHNIQUES

▶ Options for Creating a Vaginal Canal: Additional Discussion

For full-depth vaginoplasty, the simplest and most reliable surgical technique to obtain skin to line the neovaginal canal space is to use penile shaft skin. Because this skin remains intact at the base and has a robust vascular supply (within Colle's fascia, which remains with the skin when the penis is degloved), it provides an essentially well-vascularized pedicled skin flap. Using this technique, called **penile inversion vaginoplasty**, the end of the penile shaft skin is sutured closed and the entire skin tube is inverted and delivered into the neovaginal canal space (Table 46–6).

Many patients, however, are circumcised, and/or do not have sufficient penile shaft skin to line a vaginal canal of generally satisfactory depth (typically 5–6.5 in.). For such patients, three options exist:

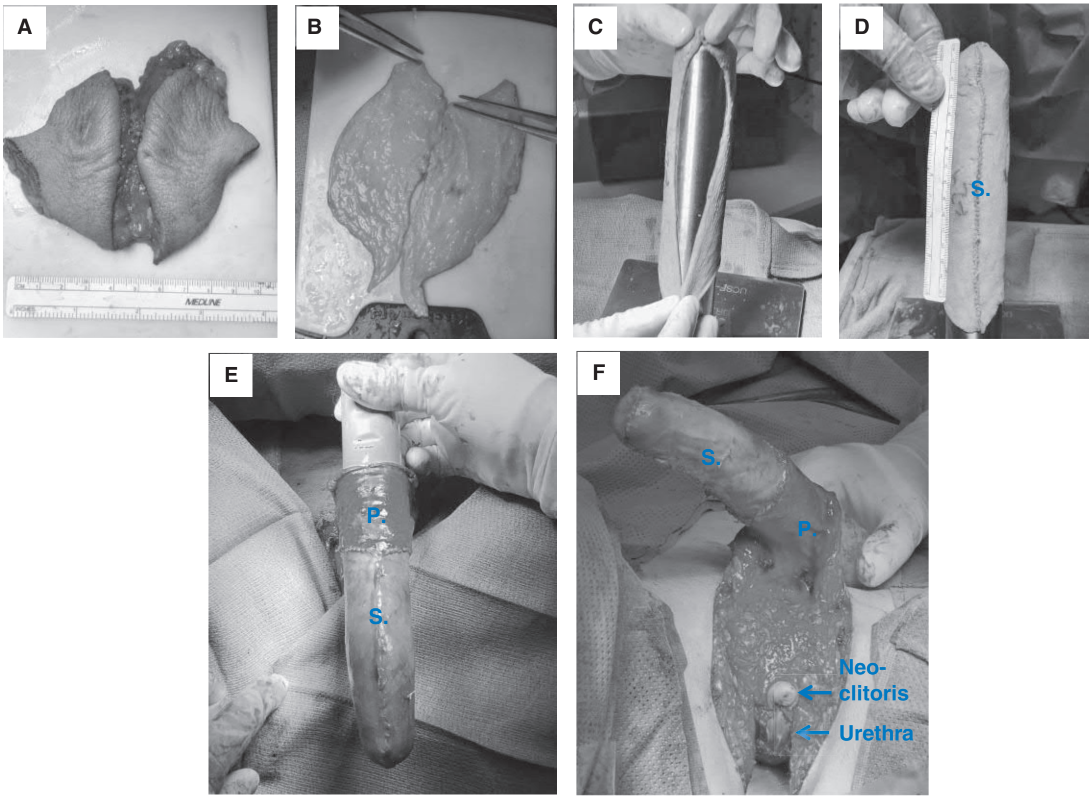
1. **Penile inversion vaginoplasty**—Only tubularized penile skin is used (see Figure 46–2).
2. ***Free* full-thickness scrotal skin grafts—**The penile skin tube is augmented with patches of full-thickness scrotal



▲ **Figure 46–4.** ***A:*** The urethral bulb is dissected to the level of the ventral aspect of the oversewn corporal stump (i.e. the new clitoral shaft). The neoclitoris is shown sutured at midline at the anterior aspect of the new clitoral shaft. ***B:*** The urethral bulb is transected sharply with dissection scissors where, on mild traction, it overlaps with the neoclitoris. ***C:*** The lumen of the urethral stump is incised along its midline ventral aspect posteriorly to the proximal bulb- where the urethral lumen turns cephalad (*blue arrow*) ***D:*** For hemostasis, the edges of the de-tubularized urethra are oversewn to the serosa of the corpus spongiosum. ***E:*** The penile skin tube is inverted and laid into the new vaginal canal space. Doing so moves the base of the penile skin tube posteriorly, and leaving the clitoris and detubularized urethra covered by dorsal penile shaft skin. A vertical incision (*ink line*) along this skin will create a window ***(F):*** through which the clitoris and urethra become visible ***(G)***. ***H:*** The anterior-most edges of skin surrounding the window are oversewn with *suture* (shown) at midline to create the anterior clitoris hood.

skin grafts (Figure 46–5A). To prepare this, the scrotal skin is defatted on a table and the skin segments then sewn together into a tube shape, which is then sutured to the distal end of the tube of penile shaft skin (Figure 46–5B). The *scrotal* skin (S) is then sewn together on a customized stand (Figure 46–5C, D) in the shape of a tube, which is then sutured to the distal end of the tube-shaped penis skin (P) to create an overall longer inverted skin tube (Figure 46–5E, F).

3. ***Pedicled* scrotal skin graft**—Ventral detubularization of the penile skin tube, with end-to end anastomosis to a sufficiently long pedicled flap of perineal and midline scrotal skin. The now-anastomosed segments of skin are then tubularized as a single unit, which is delivered into the neovaginal canal space.
4. **Intestinal vaginoplasty**—This is created by using a segment of intestine to line the vaginal canal space. While some use small bowel or sigmoid colon for this, our experience suggests that the right colon is more reliable. Colon vaginoplasty can also be offered to cis-gender women who have lost their vaginal canal to scarring from surgical and medical treatments or because of a congenital condition. An advantage of the right colon vaginoplasty that we perform is that the graft (colon segment) is supported by a robust vascular pedicle, making it usable in conditions of considerable collateral scarring or radiotherapy-induced



▲ **Figure 46–5.** ***A:*** Scrotal skin can be harvested as two separate pieces. The full-thickness skin graft is then de-fatted to the level of the Dermis. ***B:*** Alternatively, at the outset of the surgery all of the scrotal skin can be harvested as a single piece, which has the advantage of requiring only a single suture line to tubularize the graft when its ventral edges are sutured together over a stent ***(C–D)***. The resulting tube of scrotal skin (S) is often between 5-7 inches long ***(E)***. The scrotal skin tube (S) is then sutured to the intact tube of penile shaft skin (P), which will be delivered into the newly created vaginal canal space.

adverse changes. The appearance to the colon-derived vaginal introitus is unobtrusive, and its pink color gives it a normal appearance.

Options 1 and 2 listed above require preoperative permanent hair removal from the scrotal skin, as the presence of hair within the neovaginal canal may likely serve as a nidus of infection, hairballs, and poor hygiene (Garcia et al, 2017; Zhang et al, 2016). If scrotal hair is dark, laser treatment can be used. Data suggest that laser treatment may be more effective than electrolysis for permanent hair removal. Because intestinal vaginoplasty is more invasive than options 1 and 2, it is best used when an adequate amount of penile shaft and scrotal skin is not available.

Complications

A major challenge to the understanding of complications and how to prevent them is the paucity of comprehensive and detailed information about surgical techniques employed, and to develop a systematic approach to reporting outcomes related to the different surgical techniques used today. The need for detail includes reporting the *absence* of specific complications. Other limitations are that most series are retrospective, based on varying and sometimes minimal follow-up.

The reported incidence (Massie et al, 2016) of major complications with vaginoplasty is low. Arguably the most dreaded complication is a rectal injury that results in a rectovaginal fistula. This injury is usually of the *anterior* aspect of the rectum, which is the posterior aspect of the vaginal canal space, and it occurs during the dissection of the vaginal canal space. Although the definitive incidence of this is not reported in all vaginoplasty outcomes series, the incidence reported ranges from 0.9% to 3% (Buncamper et al, 2016; Cristofari et al, 2019; Rossi Neto et al, 2012). The need for blood transfusion following surgery has been reported to be 5–15% (Buncamper et al, 2016; Rossi Neto et al, 2012).

The incidence of complete stenosis with functional loss of the vaginal canal ranges from 2.9% (Buncamper et al, 2016) to 7–8% (Rossi Neto et al, 2012; Cristofari et al, 2019), although some authors distinguish between complete functional loss of the vaginal canal versus incidence of symptomatic and sometimes reversible stenosis of the vaginal canal ranging from 12% to 39% (Rossi Neto et al, 2012; Goddard et al, 2007).

Obstructive urinary complications range from 1-40%, and are typically due to stricture of the urethral meatus and an upwardly deflected urinary stream that causes wetting of the inner thighs during voiding (Cristofari et al, 2019; Rossi Neto et al, 2012; Goddard et al, 2007).

Other complications that have been noted to occur but are reported in relatively few series include prolonged vaginal pain (22% [Massie et al, 2018]), anorgasmia and clitoral hypersensitivity (52% [Cristofari et al, 2019] and 14% [Goddard et al, 2007]), and symptomatic intravaginal hair growth (29% [Cristofari et al, 2019; Goddard et al, 2007]).

Other more minor complications that are more commonly described relate to wound healing: granulation tissue of the vulva or vaginal vault (7–26%) and wound separation (5–33%) (Cristofari et al, 2019; Rossi Neto et al, 2012; Massie et al, 2018; Gaither et al, 2018).

Other Considerations

Patients undergoing vaginoplasty with or without a canal should be taught to perform Kegel exercises. Because the vaginal canal and the urethra pass through the pelvic floor muscles. It is essential that patients learn to effectively relax their pelvic floor muscles. Uncontrolled contraction, in addition to failure to adequately relax these muscles, will result in difficulty with voiding (and may contribute to sprayed urinary stream), and pain or difficulty with vaginal dilation.

Patients are also reminded that the prostate gland and seminal vesicles are *not* routinely removed with vaginoplasty for several reasons. Prostatectomy is associated with a non-negligible risk of urinary incontinence, and the prostate gland immediately abuts the neovaginal canal anteriorly. Removal at time of vaginoplasty would not only be challenging owing to the typically smaller size of the prostate gland after a long period of estrogen and androgen blockers), but would also place the viability of tissues used to create the vaginal canal at risk (increased risk of local bleeding, risk of urinary leak). As a result, patients may still note ejaculate with orgasm. We remind patients that the prostate also continues to be a potential source of erogenous stimulation during vaginal-receptive sexual activity.

Because patients retain their prostate gland, it is still possible to develop **prostate cancer**. While it is not yet known how the risk of prostate cancer among transgender women compares to that for cis-gender men, the risks and benefits of routine screening with PSA and digital exam should be discussed, with special consideration for transgender women with greater risk factors for prostate cancer (including family history and commencement of feminizing hormone therapy later in life). Because the neovaginal canal skin abuts the prostate gland, any definitive prostate cancer treatment after vaginoplasty (prostatectomy or radiotherapy) would risk direct injury and compromise the blood supply to an existing neovaginal canal.

Masculinizing (Female to Male [FtM]) Genital GAS

Patients may seek one or more common goals with masculinizing genital surgery. They may prioritize the following goals, or risks associated with these goals, differently:

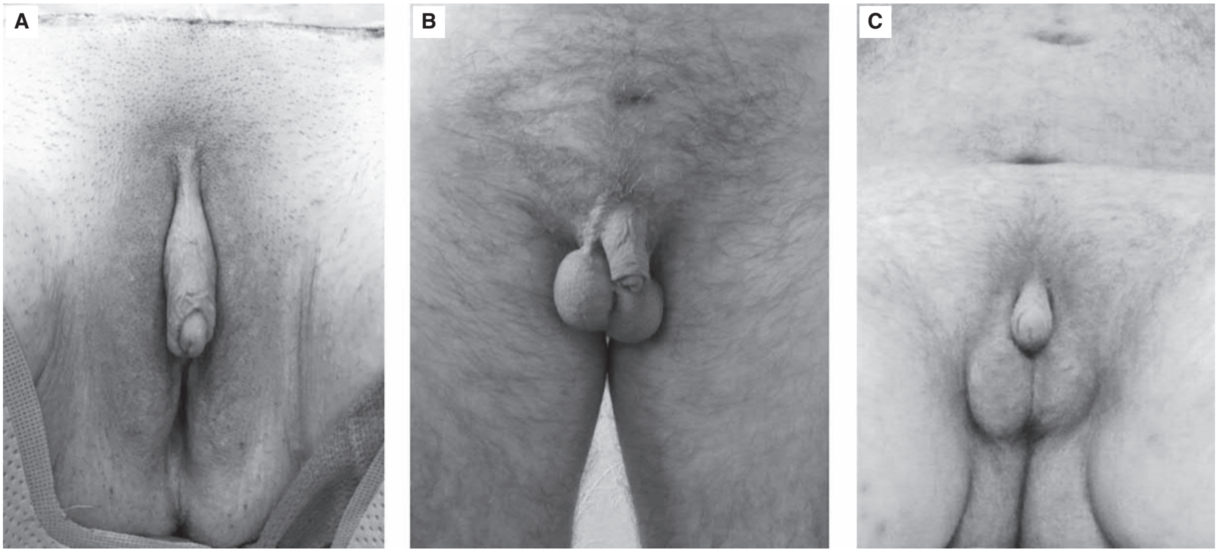
1. Elimination of *female*-appearing external and internal genitalia
2. Creation of a full-size penis
3. Creation of a scrotum containing testes
4. Ability to stand to urinate
5. Ability to achieve penetration during intercourse
6. Erogenous sensation within the penis to achieve orgasm (Rachlin et al, 2017; Garcia et al, 2014)

Surgery options can be divided into those that yield a **micropenis** (<2.5 standard deviations below mean adult penis length, or <7 cm length), made from the patient's own virilized native clitoris glans/shaft, or, a full-size phallus of dimensions on par with an average adult penis. Such a phallus is made de novo using skin and adhering adipose tissue harvested from the patient's own body. By common current terminology these surgeries are referred to as **metoidioplasty** and **phalloplasty**, respectively. Both surgery options have distinct benefits, limitations, and risks for complications. Patients today have a multitude of surgical options for these surgeries.

A. Metoidioplasty

With this surgery a penis is created from the clitoris hypertrophied by the virilizing effects of testosterone therapy.

Metoidioplasty can be performed with or without a urethral lengthening. With urethral lengthening, the native urethral opening is placed into continuity with the tip of the micropenis, using either buccal mucosa (onlay) grafts in a staged fashion, or with fasciocutaneous skin flaps using clitoris shaft skin flaps. We perform urethral lengthening in two stages. In the first stage, immediately after transection, the dorsal suspensory ligaments are incised (to release the clitoris and gain overall length), and the ventral plate of the clitoris is incised at its widest location using an H-shaped incision. The clitoris shaft is placed into traction, opening the incision to allow us to define the resulting defect's maximal area. Buccal mucosa graft is laid in the center of the defect. It is important to incise the clitoris glans as needed and lay sufficient buccal mucosa graft to ensure that a minimum 2-cm-wide strip of hairless epithelium will be present up to midglans, so that there is sufficient tissue to tubularize the neourethra later at second-stage surgery. The clitoral shaft is not degloved at



▲ **Figure 46–6.** Metoidioplasty, *with* urethral lengthening, but *without* scrotoplasty or bilateral testicular prosthesis implant ***(A)***, and *with* scrotoplasty and bilateral testicular prosthesis implant ***(B, C)***.

this time. At first-stage surgery, we also perform V,Y-plasty to transpose the anterior ends of the labia majora inferiorly, from above to below the level of the base of the micropenis. This renders more "male-appearing" cosmesis and accentuates the micropenis length.

At second-stage surgery (typically 4 months later), a ~2-cm-wide midline strip of hairless epithelium (that includes the now healed buccal graft), extending from the native urethral meatus to the glans tip, is tubularized. The clitoris shaft is degloved along its ventral and lateral borders, allowing the surgeon to transpose redundant dorsal skin to the ventral aspect of the shaft. Labia minora skin is mobilized and trimmed, so that the resulting micropenis has the appearance of a penis.

Alternatively, some surgeons perform metoidioplasty in a single stage using clitoral shaft or labia minora skin as pedicled flaps.

Vaginectomy, scrotoplasty, and testicle prosthesis placement are other options that patients may elect to undergo. We perform vaginectomy (obliteration of the vaginal canal space, with or after previous hysterectomy) and scrotoplasty at second-stage surgery. With scrotoplasty, the labia minora skin is excised and the inferior margins of the labia majora are transposed anteriorly (V,Y-plasty), creating redundant scrotal skin. Note that the anterior and posterior labia skin ends should not be transposed simultaneously, as doing so will compromise both sites of their blood supply simultaneously, and thereby increase the risk of scrotal skin loss. The medial edges of the labia majora are then sutured together at midline. The result (Figure 46–6) has the appearance of a scrotum. Testicle prosthesis can be performed safely at a separate third surgery, or potentially, at second-stage surgery.

Metoidioplasty can also be performed without urethral lengthening. At second-stage surgery, the native urethral opening can be extended to reside immediately posterior to the inferior edge of the scrotum.

The principal advantage of metoidioplasty is that it creates a penis without requiring harvesting of donor skin. Micropenis sensation is typically unchanged from presurgery. Potential relative disadvantages include the smaller size of the micropenis, and, the fact that there are no penile prosthetics yet available for the micropenis.

B. Phalloplasty

With phalloplasty, a full (adult)-size phallus can be created, but this requires use of a relatively large area of skin from elsewhere on the patient's body, and (ideally) bearing a robust blood supply (Table 46–7).

Table 46–7. Phalloplasty options to create a full-size phallus and urethra.

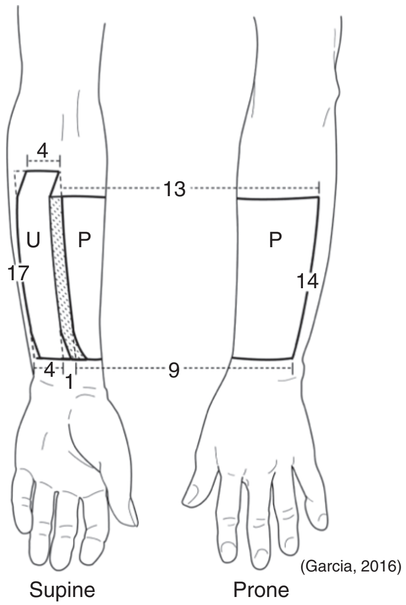
1. Radial artery forearm [free] flap (RAFF) (+/– neourethra)
2. Anterior Lateral Thigh (ALT) pedicle or free flap (+/– urethra)
3. Suprapubic (SP) skin pedicle flap
4. Groin (G) pedicle flap (– urethra*)

*While this pedicle flap does not have adequate blood supply to support a neourethra, in a separate surgery, radial artery urethroplasty can be performed to create a neourethra.

C. Radial Artery Forearm Flap

The radial artery forearm flap (RAFF) is a free flap based on the radial artery and brachial and cephalic veins of the forearm.

In 1984 Chang and Hwang were the first to describe use of a single free fasciocutaneous flap, composed of skin and subcutaneous adipose tissue from the forearm and based on the forearm radial artery and medial and lateral antebrachial cutaneous nerves to create both a sensate phallus and a urethra (Garcia et al, 2017; Chang and Hwang, 1984) (Figure 46–7).



▲ **Figure 46–7.** Radial artery forearm flap donor site markings. The urethral (U) and phallus (P) segments are harvested as single flap. A 1-cm-wide segment separating U and P skin segments is de-epithelialized (shaded area) to allow the U segment to be tubularized (skin side inside) and reside within the center of tubularized P segment (tubularized with skin *outside*). The U segment is typically 17 × 4 cm and the P segment is 14 cm long × 13 to 9 cm wide (proximal flap width is 13 cm, mid flap width 11 cm, distal flap width 9 cm).

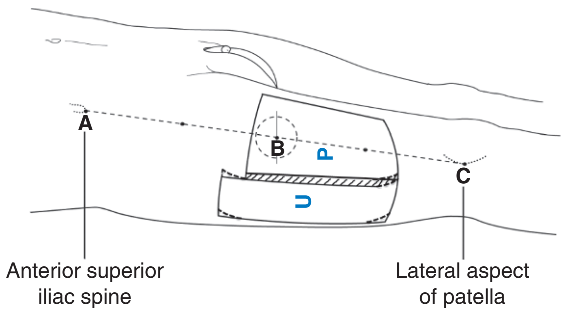
For phallourethroplasty as the first of a two-stage approach, the proximal end of the neourethra is anastomosed to the skin just lateral to the base of the clitoris shaft, and it is not until the second-stage surgery that the skin between the native urethral opening and the proximal end of the neourethra are tubularized into a single tube structure.

The dimensions shown are common, but may vary by surgeon. Some surgeons prefer two-stage over single-stage surgery. (Reproduced with permission from Garcia MM, Thomas P, Christopher NA, et al: Genital Gender Affirming Surgery for Transgender Patients. *AUA Update Series,* 2017; 36: Lesson 5.)

D. Anterior Lateral Thigh (ALT) Flap

Phalloplasty with a pedicle ALT flap, as described originally by Song and colleagues (Garcia et al, 2017; Song et al, 1984), uses a fasciocutaneous flap from the anterior lateral thigh over the vastus lateralis muscle (Figure 46–8). Its arterial blood supply originates from muscle perforators from the descending branch of the lateral circumflex femoral artery that reach the skin flap through the vastus lateralis muscle (Garcia et al, 2017; Wei et al, 2002). The lateral femoral cutaneous nerve provides innervation. As a pedicle flap, the entire flap is passed under the rectus femoris and sartorius muscles to the recipient site, where it is then used to construct the neophallus and neourethra. The ALT flap can also be harvested as a free flap.

With both flap types, a relatively smaller (~4 cm wide) portion of the flap (Figures 46–7 and 46–8) is used to construct the neourethra. It is tubularized with skin facing the lumen, and the larger remainder of the flap is rotated circumferentially around the neourethra (with the skin facing outward) to create the phallus shaft.



▲ **Figure 46–8.** The dimensions and design of a single anterior lateral thigh (ALT) flap that will yield both a phallus (P) and urethra (U) are identical to those used when the flap is harvested from the forearm. The portion of the flap dedicated to serve as the neourethra can be lateral to the portion of the flap that will make the phallus shaft (shown), or medial to it. The urethral and phallus portions are joined by a position of the flap that is deepitheliated (shaded area). The blood supply to the ALT flap comes from perforator vessels from the descending branch of the lateral circumflex femoral artery, and typically perforate through the vastus lateralis muscle. These enter the flap within a 3 cm circumference to point ***B*** (*hatched-line circle*). Point ***B*** is always the *half-way point* between the anterior superior iliac spine ***A*** and the lateral aspect of the patella ***C***. The location of the perforator vessels is determined by Doppler ultrasound *before* making any incisions to outline the flap. Once the location of the perforator vessels is known, the flap is oriented around these such that the perforators enter the flap close to what will be the proximal end of the phallus/urethra.

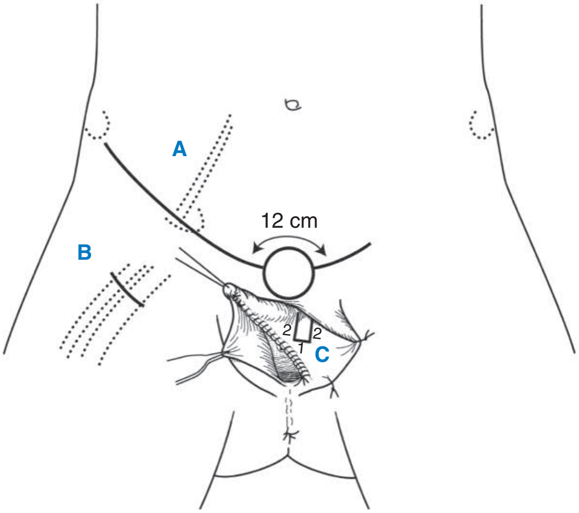
A 1-cm-wide strip of skin between the portions of the flap used to construct the urethra and the phallus shaft is deepitheliated so it can serve as a *hinge* between the tubularized phallus portion of the flap and the urethra portion located deep in the center of the resulting "tube within a tube."

With the ALT flap, the exact location of the flap on the thigh is based on the location of the perforator vessels that originate in the descending branch of the lateral circumflex femoral artery and pass through muscle (usually the vastus lateralis) before entering the flap. The flap is centered over these perforator vessels, to ensure that they are incorporated into the flap at its proximal end and close to the neourethra (Figure 46–8).

It is possible to construct only the phallus without a neourethra (eg, a patient may elect to undergo urethral shortening with perineal urethrostomy, instead of lengthening). For this procedure, a smaller flap area is used.

After transfer to the recipient site (Figure 46–9), the flap artery can be anastomosed to either one of the inferior epigastric arteries (our preference), or directly or indirectly to the femoral artery. Flap veins (basilic vein and/or cephalic vein, and/or Venae Comitans) are anastomosed to local veins including the inferior epigastric veins or the ipsilateral saphenous vein branches (Garcia et al, 2017) (Figure 46–10).

The donor site can be covered by full-thickness skin grafts (FTSGs) harvested bilaterally from the inferior buttock crease (Garcia et al, 2014, 2017); a more commonly used option is to prepare split-thickness skin grafts (STSGs) from the anterior thigh(s). Our experience in comparing cosmesis outcomes with both STSG and FTSG finds that inferior gluteal fold FTSG offers several advantages, including superior cosmesis at both the FTSG donor site and the phalloplasty flap donor site.



▲ **Figure 46–9.** Neophallus and neourethra recipient site markings for two-stage free-flap phalloplasty. Incision (bold lines) is made between the anterosuperior iliac spine and pubic tubercle, and joins a circular incision of 12–13 cm circumference at the neophallus implant site.

The inferior epigastric artery ***(A)*** can be dissected and rotated to the recipient site to provide arterial supply to radial artery of neophallus.

Alternatively, saphenous artery and vein branches can be mobilized via a horizontal incision in the sub-inguinal region over the femoral vessels. ***(B)*** In stage I of a two-stage phalloplasty, the Labia Minora ipsilateral to the site where the neourethra will be implanted is resected, and a 2 × 1 cm skin flap of hairless labia minora skin (shown on left) is incised. ***(C)*** The inferior end of this small flap is spatulated to the proximal end of the neourethra.

In a one-stage phallourethroplasty, the neophallus neourethra is anastomosed to the *pars fixa neourethra* (tubularized vaginal skin) that connects the native urethral opening to the proximal end of the neophallus neourethra).

(Reproduced with permission from Garcia MM, Thomas P, Christopher NA, et al: Genital Gender Affirming Surgery for Transgender Patients. *AUA Update Series,* 2017; 36: Lesson 5.)

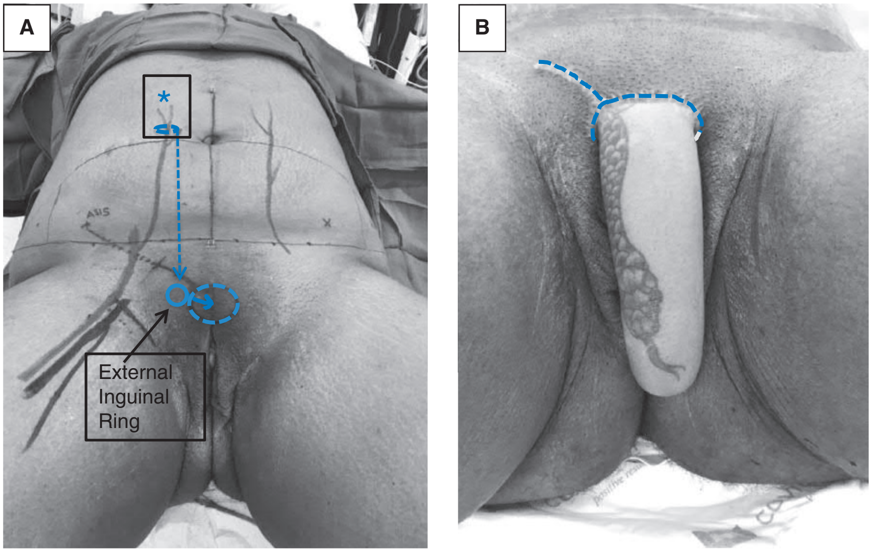
E. Suprapubic and Groin Flaps

Skin and adipose tissue from either the midline suprapubic or groin areas can be mobilized and fashioned into a phallus. For the **suprapubic (SP)** flap, the cephalad and lateral aspects of the flap are dissected and the skin/adipose tissue of the flap is lifted off of the anterior abdominal wall, leaving only the caudal end of the flap in continuity with surrounding skin. The ~14-cm-long × 12-cm-wide flap is tubularized by suturing the lateral edges of the flap along the dorsal midline; the cephalad end of the flap becomes the distal end of the phallus. This flap is supplied by local suprapubic skin perforator vessels.

A **groin (G) flap** is an approximately rectangular flap that runs parallel to and is centered one fingerbreadth *below* the inguinal ligament. It is also known as a **SCIP** flap because its blood supply is based on **superficial circumflex iliac artery perforator** branches located just medial to the sartorius muscle at the inguinal ligament and course laterally. After the flap is lifted, it is rotated 180° (the lateral end becomes medial) and is passed beneath intact skin (medial limit to the flap donor site) just lateral to where the base of the phallus will be. The **lateralmost** end of the flap at the donor site becomes the distal end of the phallus.

For both SP and G flaps, the mobilized portion of the flap is **insensate**, owing to disruption of local sensory nerves during mobilization. Patients report tactile-only sensation to the phallus only along 2–3 cm of its base (Garcia et al, 2014, 2017).

Also, because both flap types are based on fine perforator vessels, neither affords skin suitably well perfused to afford a portion of the flap to be dedicated to construction of a neourethra ("tube within a tube," similar to the



▲ **Figure 46–10.** ***A:*** Phalloplasty recipient site. The right (or left) inferior epigastric artery and two *Venae comitans* veins can be mobilized cephalad from where they traverse the inguinal ligament. The cephalad ends are transected as distal as possible (*) where they enter into the Rectus abdominus muscle and are passed via an opening made through the ipsilateral external inguinal ring (*light solid blue circle*), to reach the phallus recipient site (*light hatched-line circle*). Here, they are anastomosed to the phallus' radial artery and ~2 veins. ***B:*** The location of the recipient site incisions at completion of Stage I surgery. By using inferior epigastric instead of femoral vessels at the recipient site, the visiblity of recipeint site scars (*hatched blue lines*) is minimized.

scenarios with RAP and ALT flaps), as the risk of ischemia or stricture of the neourethra is exceedingly high (Garcia et al, 2014, 2017).

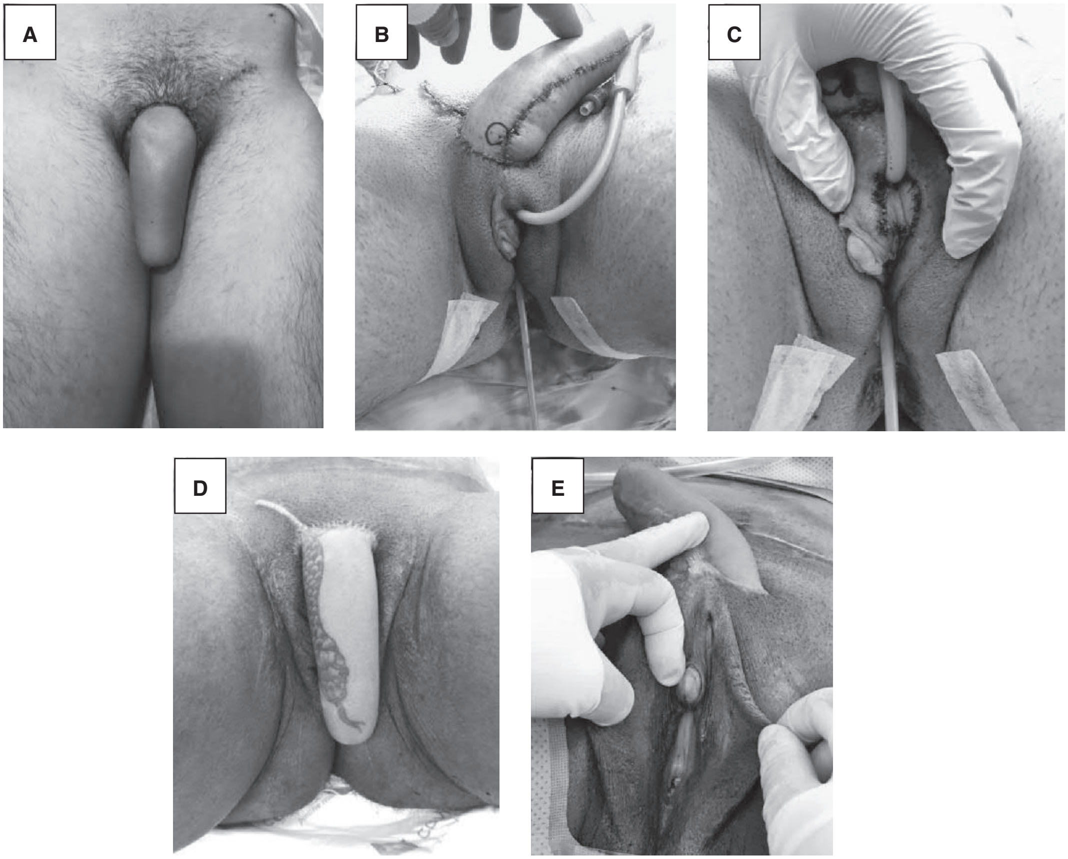
Staging of Surgeries

Metoidioplasty and phallourethroplasty can be done in one or two stages. We believe that a two-stage approach offers better, more reliable, and more cosmetically favorable outcomes. Penile prosthesis placement is always done as a separate standalone surgery, and only once it is clear that the patient is free from recurrent infections, and from risk factors for local and/or urinary tract infections (eg, elevated postvoid residuals), will no additional genital surgeries be planned. A minimum 4-month interval between stages allows adequate time for wound healing. This window can be extended to accommodate smaller surgeries to address complications between stages. Table 46–8 shows our staging plan and lists all the additional procedures that patients undergo with phallourethroplasty. Figure 46–11 shows the appearance of the neophallus/neourethra immediately after stage I and immediately before stage II. Figure 46–12 shows the appearance of the phallus at the end of stage II surgery. Figure 46–13 provides surgical details about how glansplasty is performed and techniques to optimize cosmesis.

Table 46–8. Surgery staging.

	Stage I Metoidioplasty (+ urethra = 2 stages; – urethra = 1 stage) (*Urologist*) Phallourethroplasty (*Urologist and Plastic Surgeon*) Radial Artery Forearm flap (sensate; + urethra) Anterior Lateral Thigh flap (sensate; + urethra) Suprapubic flap (insensate; – urethra)
4 mo.	
	Stage II (*Urologist*) +/– Combine with Laparoscopic hysterectomy Urethral join-up to neophallus neourethra *OR* Perineal Urethrostomy Vaginectomy Clansplasty* Transposition of micropenis (ie, native clitoris) to base of phallus*
4 mo.	
	Stage III (*Urologist*) Penile prosthesis placement (Inflatable)* Testicular prostheses placement

*With phalloplasty only.



▲ **Figure 46–11.** ***(A)*** Neophallus and proximal neourethra opening ***(B, C)*** immediately after Stage I phallourethroplasty surgery. The phallus neourethra opening is located at the left base of the natal clitoris ***(B, C)***. Note that the left Labia minora has been surgically removed. ***(D, E)*** The same structures (in a different patient) 4 months later, immediately before Stage II surgery.

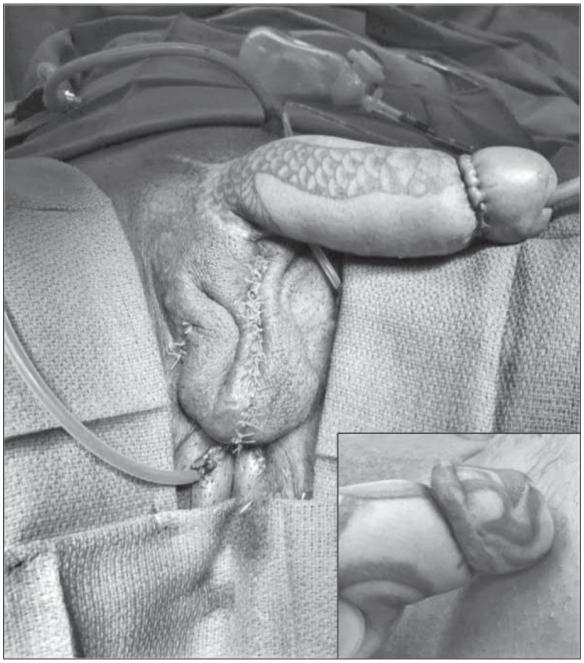
▶ Specialist Surgeons

Stage I surgery generally requires two surgeons and is best performed in collaboration with a plastic surgeon for elevation of the flap and microsurgical vascular and nerve anastomosis. In our practice the urologist performs the other aspects of the surgery, beginning with designing the flap on the donor site, and preparing the recipient site (including steps shown in Figure 46–10: dissection of the right inferior epigastric vessels and creation of a passage through the right inguinal canal for their passage to the recipient site, and, harvest of the right clitoral nerve). **Stage II** surgery can be performed by a urologist alone, although some centers may collaborate with a plastic surgeon and/or a gynecologist. In **stage III** surgery, insertion of urologic prosthetics is commonly performed by a urologist. Given that nearly all long-term complications relate to the urinary tract and/or sexual function, it is important that a urologist play an active role in presurgery planning and design as well as be directly involved in the surgeries themselves and in long-term care of the patient.

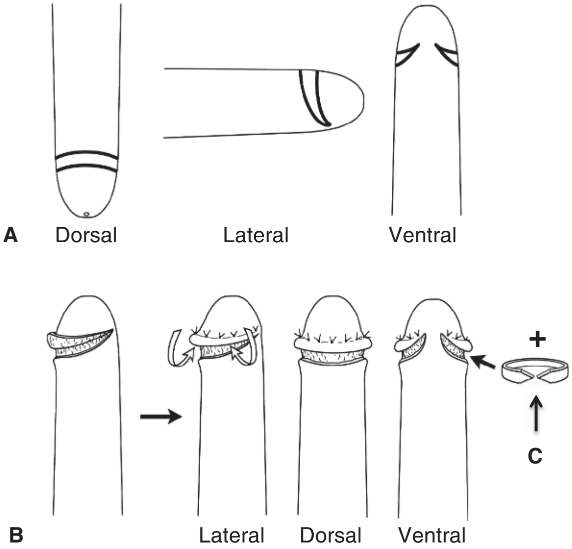
▶ Benefits and Limitations of Flap Types

The most attractive feature of the ALT flap for phalloplasty is that the donor site on the thigh is less visible than the forearm.

The primary limitation associated with the ALT flap is that the flap tends to be fairly thick, which can often result in a barrel-shaped and overly thick phallus. Indeed, excessive phallus girth results in an inability for the patient to have adequate penetrative intercourse with the phallus (pain for partner), and, the weight of such a heavy phallus often pulls the entire phallus too far posteriorly on the pubic area (Isaacson et al, 2017). Isaacson et al (2017) suggest a maximum final phallus girth of ≤12–14 cm. ALT flaps also typically do not have prominent sensory nerve bundles for nerve anastomosis.



▲ **Figure 46–12.** Surgical site at completion of of Phallo-urethroplasty Stage II. The following procedures are completed in Stage II: (1) Suprapubic catheter placement; (2) Vaginectomy (wound drain shown exiting site); (3) The native urethral opening has been rendered in continuity with the neophallus neourethra ("urethral join up"), (4) Complex scrotoplasty, to excise the Labia minora, move the posterior ends of the Labia majora anteriorly, and join the medial edges of the Labia majora at midline; (5) Transposition of the native clitoris to the *right* ventral base of the phallus (to render it not visible); (6) Glansplasty, to create a penile glans; (7) Urethral catheter placement. ***(Inset):*** Glansplasty site after healing. To achieve the narrowness at the sulcus between the distal shaft and the coronal-ridge of the glans, the skin strip graft described in Figure 46–13, C is sutured to the terminal ends of the glansplasty incision line under tight stretch such that the circumference of the skin-strip is *less than* the circumference of the distal shaft or the glans itself. This key step helps to create a cosmetically favorable glans sulcus.



▲ **Figure 46–13.** With glansplasty, we raise local skin flaps at the end of the neophallus, to create a coronal ridge and the natural appearance of a glans. ***A:*** *Incision markings:* Two curved ink lines (1 cm. apart at dorsal midline) are made on the dorsum of glans site. These are extended ventrally and taper to fuse at the ventral-lateral aspect of glans. ***B:*** *Incisions:* Only the proximal line is incised with a scalpel. The proximal skin edge is undermined (between the dermis and subcutaneous fat) *distally,* to the distal line. The *distal* edge of the skin incision is then folded inward and sutured to dermis of its own undersurface (at the distal ink line marking). ***C:*** A 1-cm wide strip of hairless skin is harvested (typically from hip area) as a full-thickness skin graft and sutured (under tight stretch, such that its circumference is less than the phallus circumference) into the defect created by the incision. Its *proximal* edge is sutured to skin of the proximal edge of the incision, and its distal edge is sutured to the skin edge of the *distal* edge of the incision (now located beneath the distal ink line). (Reproduced with permission from Garcia MM, Thomas P, Christopher NA, et al: Genital Gender Affirming Surgery for Transgender Patients. *AUA Update Series,* 2017; 36: Lesson 5.)

The radial artery forearm flap is now commonly considered the gold standard for phalloplasty because (1) its vasculature provides typically robust blood supply to the flap tissues; (2) the flap is well innervated with relatively prominent sensory nerves that can be anastomosed to native, local nerves; and (3) the flap thickness is fairly uniform, which makes resulting size and cosmesis more reliable. The principal drawback to this flap is that the forearm donor site is visible.

EROGENOUS SENSATION AND SEXUAL FUNCTION

▶ Radial Artery Forearm and ALT Flaps

Tactile and erogenous sensation can be preserved by anastomosing the dominant sensory nerve ends located along the phallus-based end of the flap to the transected proximal end of *one* of the two ipsilateral clitoral nerves (Garcia et al, 2014, 2017; Garaffa et al, 2010). While the distribution of resulting tactile sensation of the neophallus can be patchy for some patients, Garcia et al showed that about two-thirds of patients who underwent radial artery forearm flap phalloplasty with clitoral nerve anastomosis could achieve orgasm with penetration with the distal half of the phallus alone, and that all patients could achieve orgasm with direct stimulation to the location of the *micropenis* (ie, native clitoris) *after* its transposition to the ventral subcutaneous space at the base of the phallus. Interestingly, these patients described postsurgery orgasm with their native clitoris to be of equal *or greater* quality than presurgery orgasm, suggesting that only one intact clitoral dorsal sensory nerve bundle is needed for orgasm, and that orgasm with genitalia in alignment with the patient's gender improves the subjective quality of orgasm (Garcia et al, 2014, 2017).

Groin Flaps

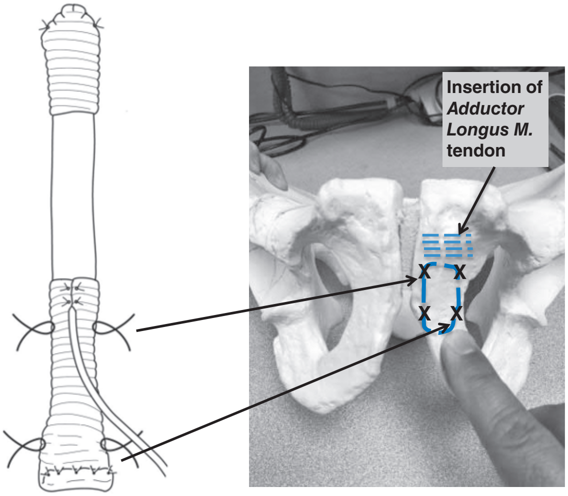
Tactile sensation in all but the 2–3 cm of the shaft base is absent. Erogenous sensation to the phallus *can*, however, be achieved by transposing the (deepitheliated) clitoris (glans/shaft) to the subcutaneous space of the ventral base of the phallus (Garcia et al, 2014, 2017).

Penile Prosthetics

Penile prosthetics provide erectile function after phalloplasty. These are placed between the neourethra and the skin surface of the phallus shaft. Surgery is performed only after phalloplasty and only in the absence of recurrent urethral strictures or fistulas, as there is no natural tissue barrier (eg, tunica or corporal compartment) within the neophallus between the urinary tract and the penile prosthesis. Also, due to a lack of corporal compartment, the prosthesis cylinder must be secured to the pubic bone to prevent migration and extrusion of the device (Garcia et al, 2017) (Figure 46–14).

While both malleable and inflatable devices can be used we have a strong preference for inflatable devices versus malleable ones, as with the latter, there is a constant force vector toward a surface of the phallus, and this increases local adipose tissue ischemia (resulting in a "flabby" phallus) and increases the risk of device extrusion through the skin. In contrast, in the flaccid state, inflatable prostheses occupy a much lower volume within the phallus and do not compress the interior of the phallus, thereby reducing the risk of extrusion and reducing ischemic necrosis of collateral adipose tissue within the phallus.

Penile prosthesis placement must avoid injuring the vascular pedicle to the phallus and urethra, which distally is centrally located, and proximally crosses towards the location of the phallus vascular anastomoses. We typically place only a single cylinder, contralateral to the side of vascular anastomoses (Garcia et al, 2017). Interestingly, a review of patients that had undergone penile prosthesis placement after gender affirming phalloplasty with transposition of the clitoris to the subcutaneous space at the neophallus base revealed that patients reported noticeably *greater* erogenous sensation after the device was implanted. We believe this is because the prosthetic serves as a "backboard" behind the clitoris and the overlying skin, which increases the stimulation that can result with direct pressure upon it through the skin.



▲ **Figure 46–14.** Inflatable penile prosthesis for a neophallus. To secure the inflatable penile prosthesis cylinder to the patient's body, the proximal and distal ends are wrapped in a "sock" and "cap" (respectively) made of Dacron (*Left*). The more proximal "sock" is sutured to a flat area of the Ischiopubic Ramus (*Right, outlined in blue*) in four locations (*marked by Black X's*), located just posterior to the insertion site of the Adductor Longus muscle tendon, using permanent (eg, 2-0 Ethibond) sutures.

SURGICAL COMPLICATIONS: GENERAL

Most complications associated with masculinizing genital gender-affirming surgery arise from two domains: urinary (urethral lengthening) and sexual function (using penile prosthetics to achieve erection).

With radial artery forearm flap phallourethroplasty, urethral strictures are reported in 15–32% and urethral fistulas are reported in 21–68% (Baumeister et al, 2011; Doornaert et al, 2011; Fang et al, 1994). The apparent higher fistula versus stricture rate likely reflects an independent incidence of focal urethral flap necrosis and/or suture line breakdown. Stricture and fistula rates are reported to be lower if local flaps, for example (eg, a vascularized labia minora skin or vagina mucosa flap) are used to construct the proximal neourethral segment (ie, proximal to the neophallus–urethra) (Kim et al, 2010). Strictures most frequently occur at the anastomosis between the phallic and the fixed part of the urethra (Lumen et al, 2011). This is probably due to suboptimal vascularization at the borders of the local and free flap where they are anastomosed.

Inflatable Penile Prosthesis

Infection of the components is reported in 8.5–12% of cases and mechanical failure in 4–18% of cases (Falcone et al, 2018; Hoebeke et al, 2010; Neuville et al, 2016). Patient dissatisfaction due to malposition of the cylinder(s) or lack of sufficient rigidity with a single cylinder has been reported in 19% of cases (Falcone et al, 2018).

ACKNOWLEDGMENTS

The author wishes to thank colleagues from the United Kingdom (Mr. David Ralph, Mr. Nim Christopher, Mr. Philip Thomas, and Mr. James Bellringer), who contributed by sharing techniques, mentorship, and collaboration to refine many of the techniques described here. The author also wishes to thank Dr. Tom F. Lue, Dr. Emil Tanagho, and Dr. Peter R. Carroll for their valuable and generous mentorship.

BIBLIOGRAPHY

AMA (American Medical Association): AMA General Policy H-185.950; Resolution 122 (A-08): Removing financial barriers to care for transgender patients, 2008. (Available online at: http://www.tgender.net/taw/ama_resolutions.pdf.)

Anton BS: American Psychological Association policy statement: Transgender, gender identity, and gender expression nondiscrimination. Proceedings of the American Psychological Association for the legislative year 2008: Minutes of the annual meeting of the Council of Representatives, February 22–24, 2008, Washington, DC, and August 13 and 17, 2008, Boston, MA; and minutes of the February, June, August, and December 2008 meetings of the Board of Directors. Am Psychol 2009;64:372. (Available online at: http://www.apa.org/about/policy/transgender.aspx.)

APA (American Psychiatric Association): Diagnostic and Statistical Manual of Mental Disorders. 5th ed., DSM-5. American Psychiatric Publishing, Arlington, VA, 2013.

APA (American Psychological Association): Answers to your questions about transgender people, gender identity and gender expression, 2011. (Available online at: http://www.apa.org/ topics/lgbt/transgender.aspx.)

Arcelus J et al: Systematic review and meta-analysis of prevalence studies in transsexualism. Eur Psychiatry 2015;30(6):807–815.

Baumeister S et al: [Phalloplasty in female-to-male transsexuals: experience from 259 cases.] Handchir Mikrochir Plast Chir 2011;43(4):215–221.

Bockting W, Coleman E, De Cuypere G: Care of transsexual persons. New Engl J Med 2011;364(26): 2559–2560.

Bockting W: Psychotherapy and the real-life experience: From gender dichotomy to gender diversity. Sexologies 2008;17(4):211–224.

Bockting WO, Knudson G, Goldberg JM: Counseling and mental health care for transgender adults and loved ones. Int J Transgend 2006;9.

Bolin A: Transcending and transgendering: Male-to-female transsexuals, dichotomy and diversity. In: Gilbert HH (ed): Third Sex, Third Gender. Zone Books, 1996.

Buncamper ME et al: Surgical outcome after penile inversion vaginoplasty: A retrospective study of 475 transgender women. Plast Reconstr Surg 2016;138(5):999–1007.

Chang TS, Hwang WY: Forearm flap in one-stage reconstruction of the penis. Plast Reconstr Surg 1984;74(2):251–258.

Coleman E et al: Standards of care for the health of transsexual, transgender, and gender-nonconforming people, Version 7. Int J Transgend 2012;13(4):165–232.

Conron KJ et al: Transgender health in Massachusetts: Results from a household probability sample of adults. Am J Public Health 2012;102(1):118–122.

Cristofari S et al: Postoperative complications of male to female sex reassignment surgery: A 10-year French retrospective study. Ann Chir Plast Esthet 2019;64(1):24–32.

Davy Z: The DSM-5 and the politics of diagnosing transpeople. Arch Sex Behav 2015;44(5):1165–1176.

De Cuypere G et al: Sexual and physical health after sex reassignment surgery. Arch Sex Behav 2005;34(6):679–690.

Doornaert M et al: Penile reconstruction with the radial forearm flap: An update. Handchir Mikrochir Plast Chir 2011;43(4):208–214.

Falcone M et al: Outcomes of inflatable penile prosthesis insertion in 247 patients completing female to male gender reassignment surgery. BJU Int 2018;121(1):139–144.

Fang RH, Lin JT, Ma S: Phalloplasty for female transsexuals with sensate free forearm flap. Microsurgery 1994;15(5):349–352.

Feinberg L: Transgender Warriors: Making History from Joan of Arc to Dennis Rodman. LGBT Thought and Culture. Beacon Press, 1996.

Fisk NM: Editorial: Gender dysphoria syndrome—the conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen. West J Med 1974;120(5):386–391.

Flores AR et al: How many adults identify as transgender in the United States? June 2016. (Available online at: http://williamsinstitute.law.ucla.edu/wp-con-tent/uploads/How-Many-Adults-Identify-as-Transgender-in-the-United-States.pdf.)

Gaither TW et al: Postoperative complications following primary penile inversion vaginoplasty among 330 male-to-female transgender patients. J Urol 2018;199(3):760–765.

Garaffa G, et al: Total phallic reconstruction in female-to-male transsexuals. Eur Urol 2010;57(4):715–722.

Garcia M: Sexual function after shallow and full-depth vaginoplasty: Challenges, clinical findings, and treatment strategies—urologic perspectives. Clin Plast Surg 2018;45(3):437–446.

Garcia MC, et al: Genital Gender Affirming Surgery for Transgender Patients. American Urologic Association, 2017. (AUA Update Series, 2017.)

Garcia MM et al: Overall satisfaction, sexual function, and the durability of neophallus dimensions following staged female to male genital gender confirming surgery: The Institute of Urology, London U.K. experience. Transl Androl Urol 2014;3(2):156–162.

Gates GJ: How many people are lesbian, gay, bisexual, and transgender? April 2011. (Available online at: http:/williamsinstitute@law.ucla.edu/wp-content/uploads/Gates-How-Many-Peo-ple-LGBTApr-2011.pdf.)

Gijs L, Brewaeys A: Surgical treatment of gender dysphoria in adults and adolescents: Recent developments, effectiveness, and challenges. Ann Rev Sex Res 2007;18(1):178–224.

Goddard JC et al: Feminizing genitoplasty in adult transsexuals: Early and long-term surgical results. BJU Int 2007;100(3):607–613.

Hage JJ, Karim RB: Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. Plast Reconstr Surg 2000;105(3): 1222–1227.

Hoebeke PB et al: Erectile implants in female-to-male transsexuals: Our experience in 129 patients. Eur Urol 2010;57(2):334–340.

IoM (Institute of Medicine): The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. National Academies Press, Washington, DC, 2011.

Isaacson D et al: How big is too big? The girth of bestselling insertive sex toys to guide maximal neophallus dimensions. J Sex Med 2017;14(11):1455–1461.

Kim SK et al: A new method of urethroplasty for prevention of fistula in female-to-male gender reassignment surgery. Ann Plast Surg 2010;64(6):759–764.

Klein C, Gorzalka BB: Sexual functioning in transsexuals following hormone therapy and genital surgery: A review. J Sex Med 2009;6(11):2922–2239; quiz 2940–2941.

Kuzon WM Jr, Gast KM: Discussion: Surgical outcome after penile inversion vaginoplasty: A retrospective study of 475 transgender women. Plast Reconstr Surg 2016;138(5):1008–1009.

Lev AI: Transgender Emergence: Therapeutic Guidelines for Working with Gender-Variant People and Their Families. 2004, Haworth Clinical Practice Press, Binghamton, NY, pp. xxix, 467.

Lumen N et al: Urethroplasty for strictures after phallic reconstruction: A single-institution experience. Eur Urol 2011;60(1):150–158.

Massie JP et al: Predictors of patient satisfaction and postoperative complications in penile inversion vaginoplasty. Plast Reconstr Surg 2018;141(6):911e–921e.

Murad M et al: Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxford, UK) 2010;72(2):214–231.

NCTE (National Center for Trangender Equality): Understanding transgender—frequently asked questions about transgender people. National Center for Transgender Equality, Washington, DC, 2009. (Available online at: http://www.transequality.org/sites/default/files/docs/resources/NCTE_UnderstandingTrans.pdf.)

Neuville P et al: Surgical outcomes of erectile implants after phalloplasty: Retrospective analysis of 95 procedures. J Sex Med 2016;13(11):1758–1764.

Pfäfflin F: Junge, Sex Reassignment. Thirty Years of International Follow-up Studies after Sex Reassignment Surgery. A Comprehensive Review, 1961–1991. 1998.

Rachlin K et al: Utilization of health care among female-to-male transgender individuals in the United States. J Homosex 2008;54(3):243–258.

Rachlin K et al: Hysterectomy and oophorectomy experiences of female-to-male transgender individuals. Int J Transgend 2010;12(3):155–166.

Rossi Neto R et al: Gender reassignment surgery—a 13 year review of surgical outcomes. Int Braz J Urol 2012;38(1):97–107.

Song YG et al: The free thigh flap: A new free flap concept based on the septocutaneous artery. Br J Plast Surg 1984;37(2):149–159.

Wei FC et al: Have we found an ideal soft-tissue flap? An experience with 672 anterolateral thigh flaps. Plast Reconstr Surg 2002;109(7):2219–2226; discussion 2227–2230.

WPATH: Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People. The World Professional Association for Transgender Health. 7th Version, 2011.

Zhang WR et al: Laser hair removal for genital gender affirming surgery. Transl Androl Urol 2016;5(3):381–387.

Zucker KJ et al: Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. J Sex Marital Ther 2012;38(2):151–189.

Zucker KJ et al: Is gender identity disorder in adolescents coming out of the closet? J Sex Marital Ther 2008;34(4):287–290.

History and Physical Examination in Pediatric Urology

47

Michael DiSandro, MD

INTRODUCTION

In pediatric urology, there are many technological advances that have created the illusion that the physical exam is not as important as it once was. For example, with testicular torsion, we now have extremely sensitive scrotal ultrasonography. This has allowed us to observe testis flow with high precision, and has led to the development of new signs such as the whirlpool sign (Esposito et al, 2014), which now makes the sensitivity and specificity of scrotal ultrasound higher than it has ever been (Agrawal et al, 2014). In the late 1990s, surgical decisions relied heavily on the physical exam, but today, they rely heavily on diagnostic imaging. This is a good thing in that it leads to overall better outcomes, but it does jeopardize the existence of the well-performed history and physical exam, and the nuances that can be learned from the exam. This chapter summarizes the art of the history and physical exam in a way that it can be used to compliment new technologies, rather than be usurped by them.

INTERACTING WITH PATIENTS AND THEIR FAMILIES

In order to be able to perform a detailed history and physical exam, patients and their families need to feel comfortable, whether in the clinic, emergency department, or as inpatients on the floor (Chiocca, 2010a). The healthcare provider needs to approach the patient and family in a calm yet confident manner. Having as much information as possible about the patient prior to the visit will help. This includes not only reviewing the medical records and imaging but also being attentive to the nurses and other providers' interactions with the family. Walking into the room blindly will make the entire visit more difficult than it need be. Once informed, the next step is meeting the family and patient, gathering the history, and performing the physical exam. For the best results, these steps need to be carried out differently depending on the patient's age, diagnosis, and other medical conditions, which will be discussed below.

All patient interactions and information are governed by the HIPAA Privacy Rule (Herold and Beaver, 2010). In addition to privacy of medical records, these rules also include verbal information that is given out to patients and their families. Before any patient information is discussed with the family, it is important to establish who the legal guardian is, and others in the room. This can be done very politely in a nonawkward way with statements such as "Hello, I'm Doctor Smith, and you are? And you?" This is also a way of breaking the ice, similar to the way one meets people in a social situation.

Finally, it should be remembered to never examine the patient prior to introductions. The patient and family should be told how the exam will proceed prior to the exam, as will be discussed below.

▶ Gathering Information

Fortunately, most pediatric urology patients are referred from primary care providers who will have done the initial history, possibly ordered some tests, and then documented in the referral exactly what they need help with. All this information should be gathered and reviewed ideally prior to visiting the patient, or after introductions in the patient's room. All radiographic images should be viewed by the provider, and relying on the radiology reports alone is not advised. Prior to the visit, a great deal of redundant information in the history can be eliminated, which saves time for both you and the patient's family. For example, if after reviewing the chart, you determine that the patient is a newborn boy with bilateral SPU grade 4 hydronephrosis, dilated ureters, and a trabeculated bladder, your main concern would be possible posterior urethral valves. Now you know the imaging and laboratory studies that the baby will need next, before even entering the room. Thus, you can limit your history to the confounding factors specific to this individual case, such as other medical problems, history of UTI and fever, medications, history of oligohydramnios, circumcision status if a boy, and family history of renal anomalies. It will not always be possible to refine your history, however, and some patients will require much more time to obtain the verbal history if there is little history to review prior to the visit.

Remember also that all new patients need a full urological history and physical exam, so even if the patient is being seen for a specific condition, a complete urologic review of systems and physical exam should be obtained. Often there are unrecognized urologic problems, such as a varicocele or recurrent UTIs, that are found and need to be addressed.

A pediatric urology-specific review of systems should include the following:

1. **General:** Fever, weight loss, lethargy, developmental milestones
2. **Gastrointestinal:** Constipation, diarrhea, nausea, vomiting, abdominal pain
3. **Urinary:** Flank pain, dysuria, hematuria, incontinence, urinary frequency and urgency
4. **Genital:** Scrotal swelling and/or pain, testicular or scrotal masses, groin bulges, phimosis, penile curvature, penile discharge, vaginal discharge

Past medical and surgical history, medications, allergies, and family and social history need to be obtained. Some medications may have urologic side effects, and certain medical conditions have associated genitourinary anomalies. Some more common examples are Down syndrome and renal anomalies, Prader–Willi syndrome and cryptorchidism, and Beckwith–Wiedemann syndrome and Wilms tumor.

Family history is important because many urologic disorders are hereditary. Some of these are the more common diagnoses seen in pediatric urology, including vesicoureteral reflux, renal cystic disease, multicystic dysplastic kidney, renal agenesis, kidney stones, nocturnal enuresis, and disorders of sex development (Arfeen et al, 1993; Murugasu et al, 1991; Eccles et al, 1996; McPherson, 2007).

Approaching the Child

It is important to interact with the child before the examination begins. The goal is to develop a relationship with the patient and family that is professional, but at the same time easing their fears and anxieties. Not only is a relaxed and comfortable child much easier to examine, but the physical exam will produce better results. For example, the testicular exam in toddlers depends on good relaxation and comfort in order to differentiate between retractile and undescended testes.

Different age groups require different approaches (Chiocca, 2010b). For babies, stranger and separation anxiety are the main anxieties that should be addressed. The parent should be allowed to hold the baby for as long as possible before the exam begins and be present at the baby's side during the exam. Approaching the baby slowly while smiling and talking in a calming voice and then allowing the parent to undress the child all help decrease separation anxiety. Once by the child's side, it is best to touch her/his hand first to show that you do not pose a threat, then slowly start the exam. The caregiver should be coddling the child from above. As soon as the exam is over, walking back across the room is helpful so the caregiver can dress and comfort the child.

For toddlers, since they are very concrete thinkers, ensuring that there are no misunderstandings is important. Use short, concrete instructions and do so in a mild, relaxing way. Incorporate their toys into the process and perform the exam as quickly and efficiently as possible.

For preschoolers, since they like to please and conform, the exam is usually easier. Have them involved in the process such as letting them dress and undress themselves.

For school-age children, they are becoming more fearful to possible injury, and their embarrassment about the exam is increasing. Explain all the steps of the exam, and don't appear rushed. Use more sophisticated language and make it seem as though the two of you are in a comfortable discussion.

For adolescents, speak to them as you would an adult. Relay the findings of your exam to them directly and ask if they have any questions. Respect their privacy and reassure them about confidentiality (Hockenberry et al, 2005). After age 16 it is important that the patient assent to their own care in addition to the parents consenting, especially if it involves genital examinations.

THE PHYSICAL EXAM

Vital Signs

Some important findings would be urinary tract infection with fever, pain with tachycardia, or renal dysplasia with hypertension.

General Findings

The patient's general appearance should be assessed. The level of comfort and/or pain should be assessed. Are there unusual odors such as occur with fecal or urinary incontinence? Are there any syndromic features?

Head, Ears, Eyes, Nose, and Throat (HEENT)

Check for preauricular skin tags, which are associated with urinary tract abnormalities (Kohelet and Arbel, 2000).

Abdomen

The abdominal exam may reveal such findings as abdominal mass, distended bladder (which is easier to palpate in infants and toddlers), fecal impaction, flank or abdominal tenderness, and umbilical drainage or masses.

Genital Exam

The appearance of the genitals in relation to the patient's overall appearance should be assessed first. The word "typical" is used to describe genitalia that match the sex of rearing, either male or female. By definition, most patients will have typical genitalia, but on occasion, the genitalia may not conform to societal definitions of typical individuals, and these patients are said to have "atypical genitalia." For example, a baby being raised as a boy who has a small phallus located below his scrotum (penoscrotal transposition) would be considered to have atypical genitalia. The diagnosis of atypical genitalia is important because these patients may have a disorder of sex development (DSD), which in some cases would require immediate attention. There are many different forms of atypical genitalia, and the workup depends on the history, physical exam, and karyotype.

Once the overall appearance of the genitals in relation to the patient is assessed, the next step is to evaluate the Tanner stage. The Tanner stage (Solorio, 2002) should be assessed with respect to the patient's age (precocious or delayed puberty), sex of rearing (DSD), medications (antiandrogens and estrogens), birth history, and the patient's menstrual history.

Performing the genital exam is important in every patient regardless of the diagnosis, especially since pediatricians often miss subtle genital findings (Singh et al, 2010). Patients in one sense are lucky to be at the pediatric urologist's office because not only will they be seen for their chief complaint, but they will obtain a complete urologic physical exam.

The specifics of the genital exam are discussed below.

A. Retractile versus Undescended Testis

The inguinal and scrotal exams are important yet difficult to perform well without experience. Many patients referred to pediatric urology with undescended testis in fact have retractile testis, it's just that the primary care provider could not tell the difference between the two. Retractile testes are not undescended testes. The length of the spermatic cord in retractile testes is normal, so the testes will easily reach the scrotum and stay there when the child is warm and relaxed, such as in a warm bath. Retractile testes do, however, have an overactive cremaster muscle, which can pull the testes up into the inguinal canal temporarily, but once that muscle relaxes, they come back down. This is normal in toddlers and young children before reaching puberty. Exam skills are imperative to distinguish between the two, because the two are treated differently. Some tricks of the trade for boys include the following.

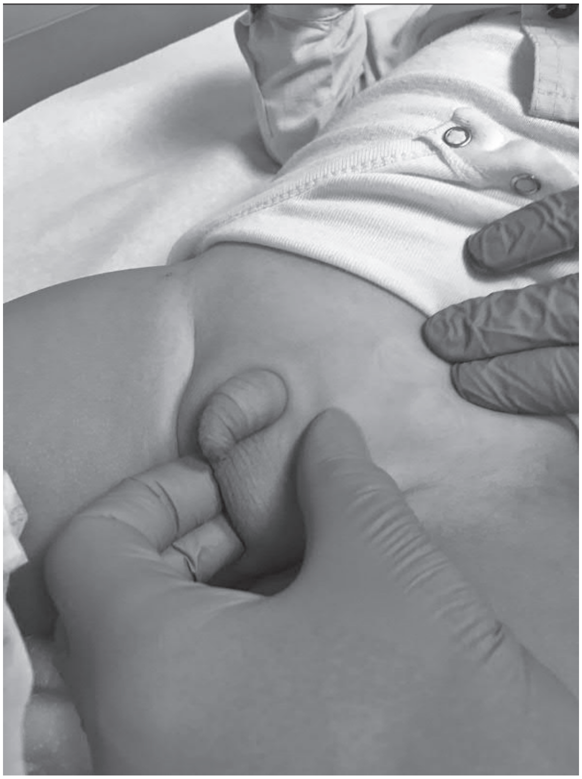
1. Obtain a good history—Ask the caretaker if s/he sees the testis in the scrotum when the baby is relaxed such as in a warm bath or when sleeping. If so, then the testes are most likely retractile. Also, ask whether the testis was in the scrotum when the baby was a newborn; the cremasteric muscle reflex is not yet developed at that time, so if both testes were descended at birth, it is more likely that they are retractile rather than undescended if the patient is older.

2. Have the patient relax as much as possible for the exam—Provide distractions such as toys or videogames. Have the caretaker coddle the child. Observe the testes visually before physically touching the scrotum. Often, the testis will be seen in the scrotum, but as soon as the scrotum is examined, they retract upward.

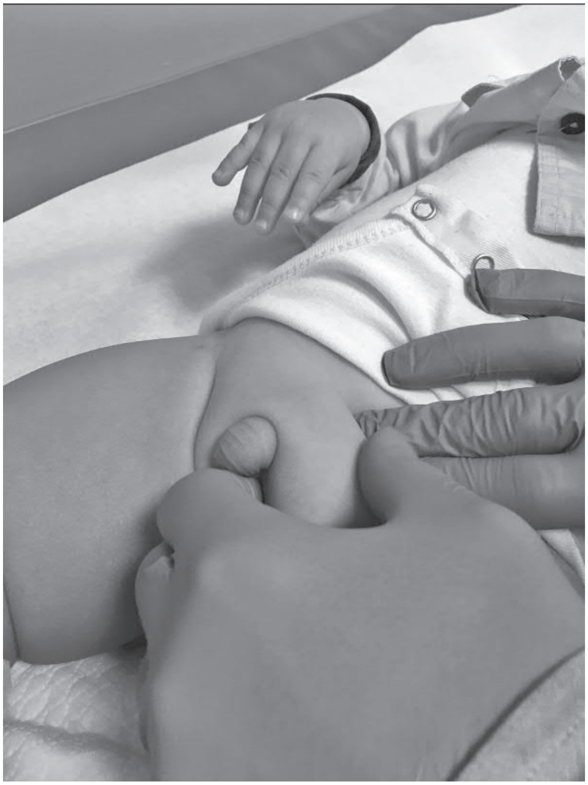
3. Use soap in the inguinal canal—This allows your hands to slip over the canal more easily and makes finding the testes easier.

4. Rotate your hand positions—If the testis is not immediately apparent in the scrotum on your initial approach (Figure 47–1), start by placing one hand just above the inguinal canal, and the other hand distal to that close to the proximal scrotum. Then, using one hand on the inguinal canal, try to milk the testis down (Figure 47–2), then hold that hand in position to prevent the testis from going back up. Then, with the other hand, try to feel the testis between your thumb and other fingers. It may take several attempts at this maneuver before the testis is felt (Figure 47–3).

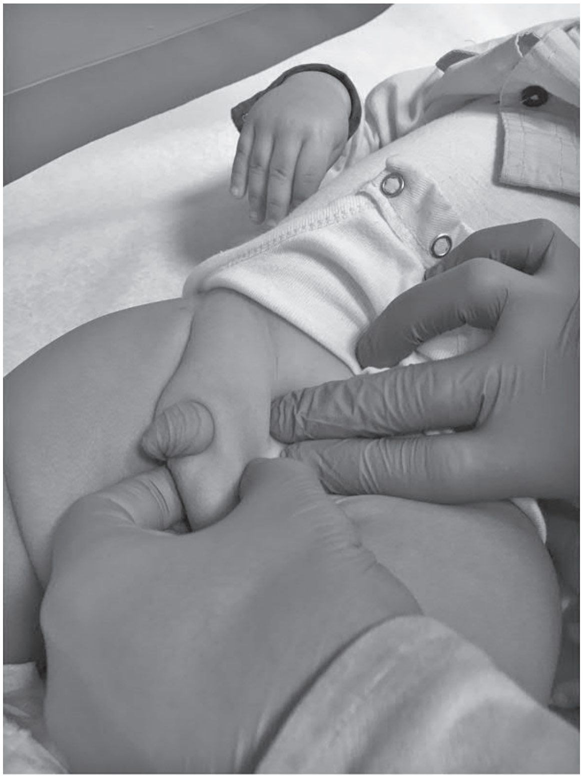
5. Milk the testis down into the scrotum—Once the testis is felt, attempt to milk it down all the way into the scrotum. If it will not reach the scrotum, then it is undescended. If it reaches the scrotum, you must release it and see if it stays there. If the patient is as relaxed as possible, and the testis



▲ **Figure 47–1.** Initial approach to the undescended testis.



▲ **Figure 47–2.** The next step is milking the testis down.



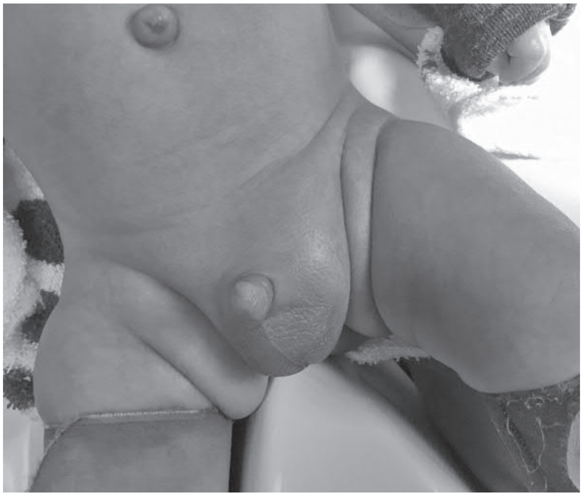
▲ **Figure 47–3.** The final step is to trap the testis below the external inguinal ring.

stays in the scrotum for a reasonable period of time, then it is retractile and not undescended.

6. Massage the inguinal canal—After you find the testis and bring it down into the scrotum, you can massage the inguinal canal with your proximal hand to try and relax the cremaster muscle. This, plus keeping the patient relaxed, will usually allow a retractile testis to stay in the scrotum.

B. Hydroceles and Hernias

The history is important to help distinguish between inguinal hernias and hydroceles, and if a hydrocele is present, to distinguish between a communicating and non-communicating hydrocele. On history, inguinal hernias are usually noticed as a groin bulge by the parents (or patient) that comes and goes on its own. It may be more apparent when the patient is crying or straining (Figure 47–4). Sometimes hernias don't resolve and can be incarcerated, which would be associated with a history of tenderness, pain, and possibly fever. Hydroceles are not painful or tender and are usually confined to the scrotum, but can extend up into the inguinal canal, or involve only the inguinal canal (hydrocele of the spermatic cord). If the groin is involved, hydroceles can be confused with inguinal hernias,



▲ **Figure 47–4.** Inguinal hernia in an infant.

and transillumination with a flashlight or performing an inguinal ultrasound can help distinguish between the two. A hernia will have abdominal contents such as fat or bowel in the sac, whereas a hydrocele will contain only fluid.

Communicating hydroceles tend to change in size intermittently; they become larger with activity or straining such as with a cough, and they become smaller when the patient is relaxed or sleeping. Noncommunicating hydroceles tend to stay the same size or slowly increase in size with time, but they do not fluctuate in size.

The age of the patient is important as prepubertal boys are more likely to have communicating hydroceles, and postpubertal boys, noncommunicating hydroceles (Wilson et al, 2008). Sometimes a hydrocele can be tense, and it will be difficult to palpate the testis. If that is the case, further imaging can be performed such as a scrotal ultrasound to determine whether a testis is within the hydrocele sac, especially if surgery is planned.

Often the parents will note a groin bulge at home, or scrotal swelling, but when the patient is examined by the pediatric urology provider, the exam is normal. This does not exclude the diagnosis of hernia or hydrocele. If in doubt, it can be helpful to have the parents photograph the scrotum when they see the bulge or swelling. Even if the hernia is not clinically present at the time of exam, if the history and pictures are convincing, then surgery can be planned. If in doubt, scrotal and inguinal ultrasound may help in the diagnosis (Wani et al, 2015).

For girls, the presentation is usually a groin bulge that the parents or patient notice, especially with straining, and as in boys, it usually reduces on its own and may not be apparent on physical exam. Again, as in boys, even with a normal exam, a strong history of a groin bulge that appears and disappears is sufficient evidence to schedule an inguinal hernia repair, especially if the parents have a photo of the groin bulge when it is present.

C. Testis and Epididymis

In addition to checking the location of the testis as discussed above, it is also important to assess the morphology of the testis. The size of the testis, especially in relation to the contralateral testis, should be assessed. If one testis is nonpalpable, the other testis may have compensatory hypertrophy. If the patient with a unilateral nonpalpable testis has contralateral compensatory testicular enlargement, it is likely that he has an absent testis on the nonpalpable side (Son et al, 2016; Hodhod et al, 2016). Testes sizes vary according to the patient's age, and there are excellent references that can be used to help determine normal testis size (Goede et al, 2016).

The entire testis should be palpated, and not just a representative portion. The testis should be homogeneous without masses or lumps. The epididymis is then examined, and it should be remembered that in older patients the epididymis can be quite sensitive, so the exam should be done thoroughly but carefully. The most common epididymal findings are epididymal cysts, which are usually nontender, small, and homogenous, and are located in the head of the epididymis (Homayoon et al, 2004; Garrett et al, 2004). Any testicular or epididymal mass should be evaluated with a scrotal ultrasound.

D. Spermatic Cord

Next, the spermatic cord is examined. In prepubertal children, a cursory exam assessing for obvious findings such as hydrocele of the cord or masses is all that is needed. After puberty, the cord should be examined for the presence of the vas deferens and the presence of enlarged veins (varicocele). The patient should be asked to stand and perform a Valsalva maneuver during the exam to see if the veins of the cord become more apparent. Often, a varicocele can be quite obvious and can be seen visually through the scrotum even before the exam begins. Varicoceles are most often on the left side, but can also be seen bilaterally, so both cords should be examined thoroughly. It is important to assess relative sizes of the testes as varicoceles are associated with testicular atrophy on the affected side (Alkaram and McCullough, 2014). Varicoceles are seldom tender and rarely painful, although they occasionally can cause mild intermittent groin or scrotal discomfort. This discomfort is different from true genital pain in that it is mild and seldom bothersome, so if the history suggests anything other than mild intermittent discomfort, other sources of pain need to be addressed such as testicular torsion, epididymitis, or inguinal hernia even if the patient has an obvious varicocele.

E. Inguinal Canal

Next, the inguinal canal is examined. In a prepubertal boy, this is done by gently palpating the groin and assessing for masses or tenderness. In postpubertal boys, the exam should be done in standing position and performing a Valsalva maneuver. One hand is placed on the groin and the other into the upper scrotum along the spermatic cord. No contents other than the cord should be felt, and there should be no bulging of the groin. In the girl, a gentle exam of the groin is all that is needed as inguinal hernias in girls are not common, and without a history of groin bulges, the presence of an inguinal hernia is not likely.

F. The Scrotum

Inflammation of the scrotum and contents may be an acute problem that requires immediate attention. The most common causes of scrotal pain and inflammation are epididymoorchitis, testicular torsion, or torsion of the appendix testis. All three conditions are treated very differently, so it is imperative to obtain a good history, physical exam, and imaging studies.

▶ Distinguishing between Testicular Torsion, Torsion of the Appendix Testis, and Epididymoorchitis

Knowledge of the patient's history is vital to help distinguish between the three different entities. The questions asked should be open-ended, such as "Tell me what happened" rather than specific, such as "Did the pain begin in the testis?"

Open-ended questions will give you more hints as to the nature of the pain, and it is the subtle differences that will help guide the diagnosis. Testicular torsion has a more abrupt onset, so the patient may state the exact time the pain started, whereas with the other two, a more insidious onset is common, and the patient may claim to have noticed some scrotal pain, and then the parents noted that the child began to walk strangely. Also, with torsion, the pain may stop the child in his tracks and cause him to lie down immediately. Sudden nausea and vomiting may occur. The parents may notice immediate redness and swelling of the scrotum and will often take the child to the emergency department immediately.

With epididymoorchitis, the pain, redness, and swelling will often increase with time until it reaches a point where the patient is so uncomfortable that he needs to be seen by a physician. Unlike with testicular torsion, there may be associated urinary symptoms such as dysuria, and there may be an accompanying urinary tract infection (UTI). The patient may also have a history of fever, urethral discharge or sexually transmitted disease (STD).

For torsion of the appendix testis, the pain is severe, but rarely extreme, as with testicular torsion. In fair-skinned children, if the examination is done early on, the provider may see a blue hue under the scrotal skin ("blue dot" sign); however, as the condition progresses, the entire testis and scrotum will become inflamed and then the exam becomes much less specific. Since the appendix testis is located on the upper outer portion of the testis, a careful exam of the inferior portion of the testis should be done. Often, the lower portion of the testis will not be tender, especially if the exam is done soon after onset of symptoms.

The cremasteric muscle reflex can also be helpful. With testicular torsion, the cremaster muscle is often tense; thus the testis may be high-riding, and the cremasteric reflex will be absent. The other finding that should be assessed is the presence of a fluctuant scrotum. This may occur with prolonged epididymoorchitis and may suggest an abscess. With testicular torsion, the scrotum is very firm, reddened and tense, and not fluctuant.

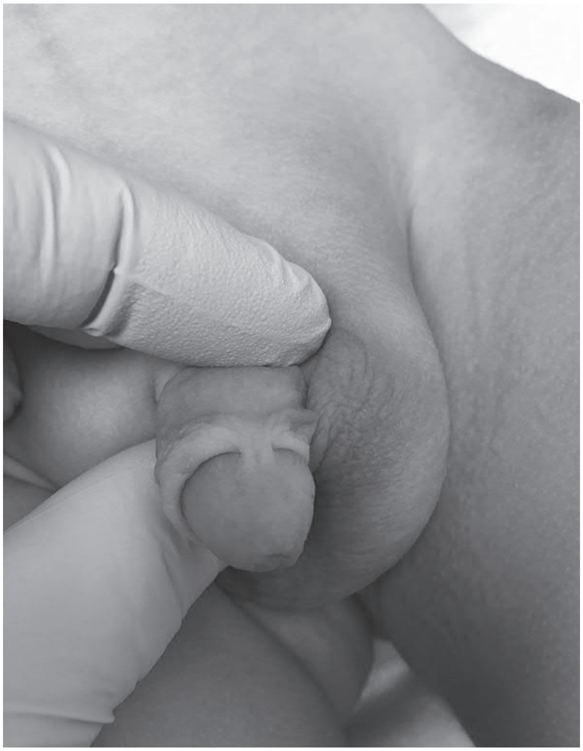
Penis and Scrotum

The overall appearance of the penis and scrotum should be evaluated first prior to palpation, looking for obvious signs of atypia such as penoscrotal transposition, bifid scrotum, and small size of the penis and/or scrotum. Then, closer inspection and palpation is performed to assess for more subtle findings such as the location of the meatus and penile curvature.

A bifid scrotum can range anywhere from a small indentation at the level of the median raphe, to a complete separation that gives the appearance of labia instead of scrotum. The severe forms of bifid scrotum are associated mainly with DSD, so there may also be severe hypospadias, chordee, and penoscrotal transposition. In these more severe cases, the term **ambiguous genitalia** can be used to describe the genitalia because the phenotype is neither typically male nor typically female. However, the word **atypical genitalia** is now preferred and the terms **typical** and **atypical** will be used throughout this chapter.

Penoscrotal transposition is also commonly seen in DSD but can often be an independent finding. In mild forms, the scrotal skin will wrap above the penis and sometimes connect back to itself superiorly. In more severe forms, the scrotum may be mainly superior to the penis, and if that is the case, the scrotum will be bifid, with the penis protruding between the two (halves) of the scrotum, appearing to be more typically female rather than male.

Examination of the foreskin is important, but it should be remembered that the foreskin may not retract at all in a newborn or young child, which is normal. The foreskin in a newborn usually covers the entire glans, and often the meatus is not seen. There is no need to force the foreskin back to examine the meatus. Phimosis in a child under 8 years of age is not worrisome if the child is voiding normally. After 8 years of age, the foreskin should retract easily, and if it does not, the patient may require treatment. Sometimes there are adhesions between the foreskin and the glans in prepubertal boys, and thus the foreskin does not retract completely. These are normal and will resolve on their own after puberty. However, if the child has had a previous circumcision, the adhesions may not resolve on their own and may even form skin bridges (Figure 47–5). These types of adhesion are abnormal and should be addressed.



▲ **Figure 47–5.** Penile skin bridge after circumcision.

Paraphimosis occurs in uncircumcised boys when the foreskin becomes trapped proximal to the glans. The history usually reveals that the patient or caretaker pulled the foreskin back and forgot to reduce it immediately. The skin then become red, swollen, and painful, and will need to be reduced either in the emergency department or in the operating room.

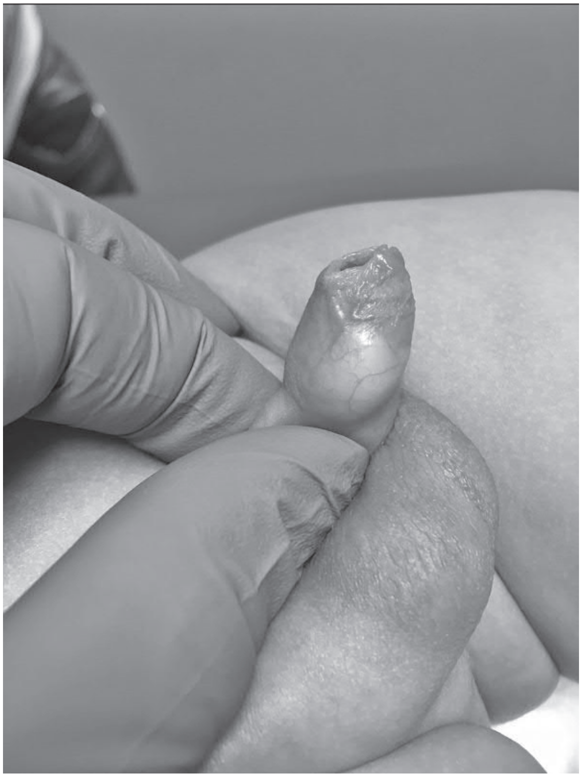
Balanoposthitis is inflammation of the foreskin and glans and can range from being mild with only irritation and redness, to being severe with edema, pain, and purulent drainage. If it is mild, treatment may consist of gentle daily cleansing, but if it is severe, treatment may require administration of topical or oral antibiotics (Shahid, 2012).

Another common finding in uncircumcised boys, and boys with an incomplete circumcision, is smegma. **Smegma** is the accumulation of sebaceous secretions and shed skin between the inner and outer parts of the foreskin, and is not life-threatening. It appears as a white mass under the skin, and may be mobile (Figure 47–6). There is no need to retract the foreskin to express the smegma, as it will usually express on its own with time.

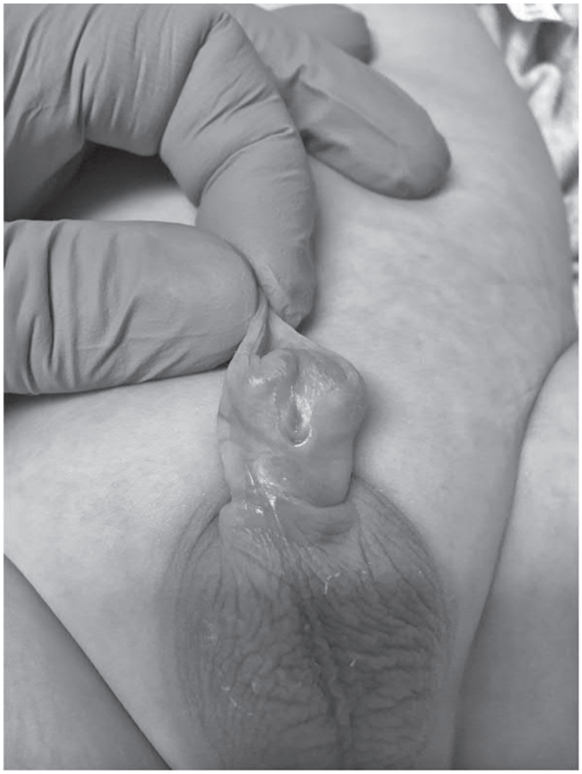
If it is noted that the foreskin does not completely cover the glans, it is usually deficient ventrally. If that is the case, the location of the meatus should be assessed because absent ventral foreskin is often associated with hypospadias. Also, the penis may be curved dorsally (chordee).

Although the meatus is normally located near the tip of the glans, the meatus can be present anywhere along the midline of the penis either dorsally (epispadias), or ventrally (hypospadias). Epispadias is part of the exstrophy–epispadias complex, so the patient may manifest symptoms of bladder or cloacal exstrophy as well. Although there is no universally accepted nomenclature for the location of the meatus in hypospadias, it is usually described as either distal, midshaft, proximal, or perineal (Figures 47–7 and 46–8). In mild cases, the parents or patient may not even notice an abnormality, and in severe cases the meatus may have a perineal location, which is often associated with a DSD.

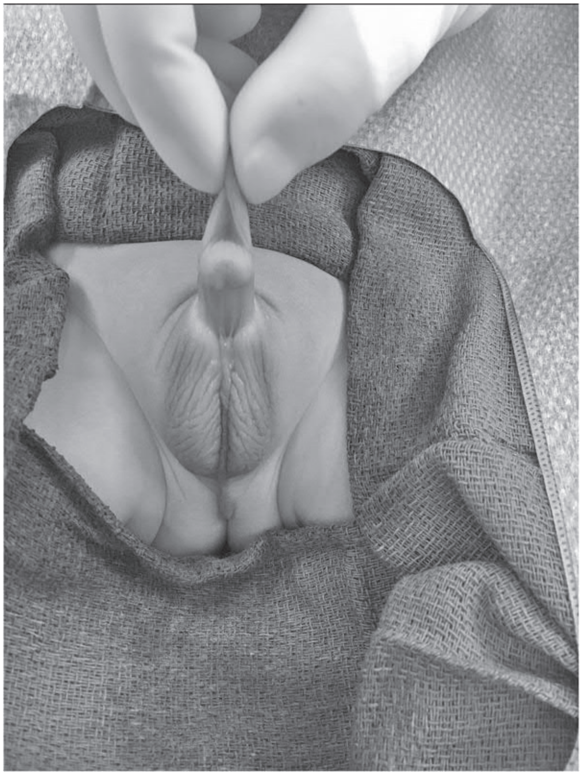
In addition to the location of the meatus, the morphology of the meatus should be assessed as well. Typically it is slit-like, but it can also be very large (megameatus), or very small (meatal stenosis). A patient with a megameatus will usually have a complete foreskin (megameatus intact prepuce [MIP]), so the megameatus may not be apparent until the child is older, or if the child is circumcised. Meatal stenosis is common in circumcised boys and appears as though the meatus is closing up ventrally. It is not concerning unless the



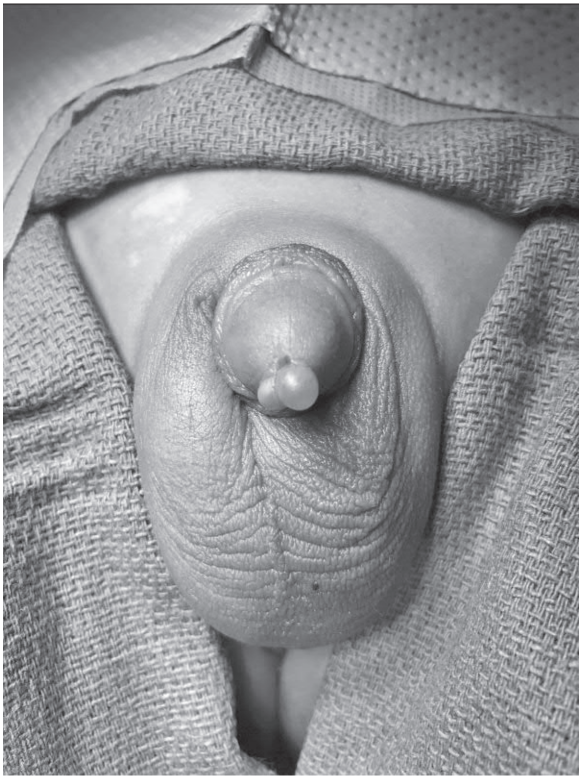
▲ **Figure 47–6.** Smegma.



▲ **Figure 47–7.** Midshaft hypospadias.



▲ **Figure 47–8.** Proximal hypospadias.



▲ **Figure 47–9.** Meatal cysts.

patient has an abnormal urinary stream (the stream may veer upward when voiding).

Rarely, the meatus is duplicated. Each meatus will be in the midline, but one will be dorsal and the other ventral (hypospadias). The ventral hypospadiac meatus is usually the functional urethra.

Meatal cysts are relatively common and have the appearance of small fluid-filled sacs located on the meatus, usually laterally, and extending a few millimeters proximally into the urethra itself. These rarely affect voiding, but often can be disfiguring and thus may require excision (Figure 47–9).

The length of the penis should be assessed. If the patient's penis appears small, a stretched penile length should be obtained. This is done by pulling the glans to stretch the penis to its maximum length, then measuring the distance from the pubic bone to the tip of the penis. If the length of the penis is less than 2.5 standard deviations (2.5SD) below the mean (Camurdan et al, 2007) for the patient's age and ethnicity, it is considered a micropenis. If the stretched penile length is normal, yet the penis appears small, it is usually secondary to a hidden penis.

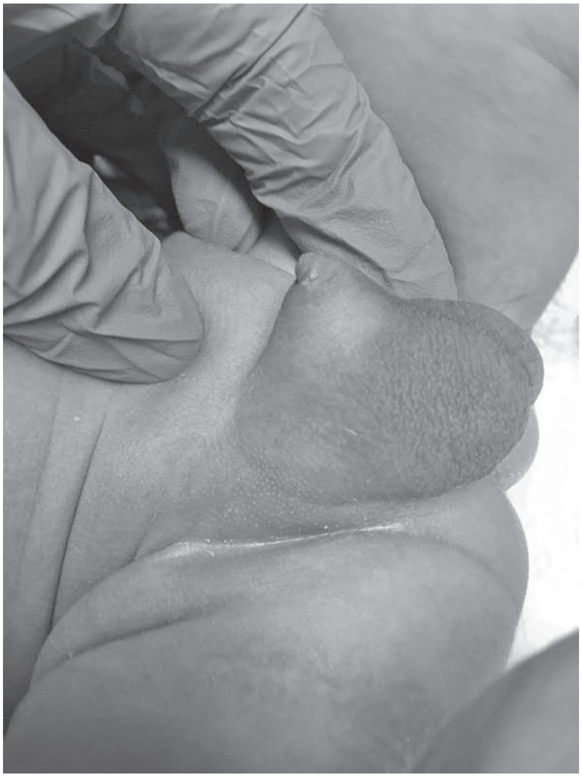
Hidden penis can occur for several reasons. First, the suprapubic fat pad may be large, and the penis may be hiding within it. This condition can also develop after a circumcision when the foreskin closes over the glans and essentially traps the penis under the fat pad. Another possible reason for a small-appearing penis is a congenital buried penis, where the foreskin appears to be separate from the body of the penis (the foreskin is anterior to the body of the penis, and the penis is pointing downward toward the scrotum) (Figure 47–10). With a buried penis, urine may be trapped within the foreskin and on examination urine may be able to be expressed with gentle pressure.

Penile torsion is another condition that may be noted on exam. The penis may be rotated to the right or left, and the median raphe may not be in the midline. Penile torsion is not a problem unless it is extreme (> 45% rotated), in which case it may need to be corrected.

Finally, the penile skin should be assessed for the presence of any masses or skin lesions, especially in a postpubertal child.

External Genitalia Exam in the Female

In the female, the external genital exam consists of an evaluation of the labia majora and minora, the vestibule, and the urethra, vagina, and clitoris.



▲ **Figure 47–10.** Congenital buried penis.

The left and right labia should be separate, and the vestibule should be open. The labia minora may be fused in the midline (labial adhesions), causing the vestibule to appear closed. When this occurs, the fusion usually begins at the posterior fourchette and extends ventrally. Labial adhesions rarely cause any problems and often resolve on their own. If they are thick, there may be only a pinpoint opening where urine exits, and that may require treatment. In young patients the vaginal introitus may not be seen secondary to the presence of the hymen.

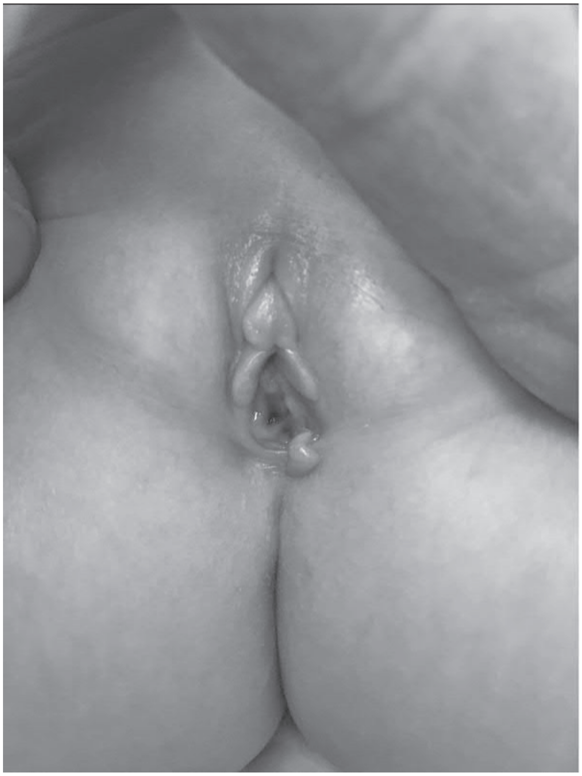
Another finding in the vestibule is urine pooling, which may suggest incontinence, vaginal voiding or less likely an ectopic ureter inserting into the vagina. History can help distinguish which of these it is. With typical incontinence there should be dry intervals between voidings or leaking; with an ectopic ureter, there are no dry intervals and the patient's underpants are always wet. Vaginal voiding usually results in wetness after voiding and then dry intervals in between.

The location of the urethra should be just anterior to the vagina, and the urethra should be separate from the vagina. If there is only one orifice seen, the patient may have a cloacal anomaly or common urogenital sinus. If the urethra is very anterior, the patient may have epispadias or bladder exstrophy.

If any interlabial protrusions or masses are noted, they should be assessed further. Interlabial masses may include prolapsed urethra, prolapsed ureterocele, paraurethral cyst, hydrometrocolpos, or rhabdomyosarcoma. A prolapsed urethra is usually friable and somewhat red-purple in color, whereas a prolapsed ureterocele is usually more cystic and fluid-filled in nature. History is also important as urethral prolapse usually occurs in patients of African-American descent (Valerie et al, 1999). Hydrometrocolpos may appear as a darkened tight cystic mass protruding from the vaginal introitus, whereas rhabdomyosarcoma is usually heterogeneous. Hymeneal tags can also present as interlabial masses (Figure 47–11).

The clitoris should be covered with a clitoral skin hood and typically does not protrude. If it does protrude, clitoromegaly should be considered. It is important to notice clitoromegaly as it can be associated with congenital adrenal hyperplasia (CAH), which in a newborn can be a life-threatening illness.

The anus should be assessed for position and the presence of an anal wink.



▲ **Figure 47–11.** Hymeneal tag.

Finally, the lower back should be examined for sacral dimples, which can be associated with spinal cord abnormalities that may lead to neurogenic bladder. A small pit in the skin at the level of the sacrum is normal, but any deep or large pits, a location that is higher than the sacrum, or other cutaneous stigmata should be assessed further as they may be associated with spinal dysraphism or neural tube defects and thus lead to a neurogenic bladder (Sy et al, 2014).

DIGITAL PHOTOGRAPHY

Since the morphology of the genitalia is so important in pediatric urology, digital photography is now commonly used to document atypical findings. Images obtained can be placed in the electronic medical record, or forwarded to other providers who can then consult remotely, such as an emergency department physician to a staff physician. The use of digital photography may decrease the number of exams needed from different providers (providers can collaborate using the images rather than actual exam), as well as visits to the emergency department for postoperative patients (the patient can forward images to the provider). However, it must be remembered that digital photography has some important caveats. First, consent must be obtained according to your institution's policy. Some institutions may have strict limits on photography, while others allow for it with secure smartphones, cameras, and servers. Second, all photography must meet HIPAA regulations as it is considered a part of the medical record, and thus must be stored on a secure phone or server that meets your institution's guidelines, and images can be transferred only between secure devices. Finally, the photography must be done in a compassionate and sensitive manner. The same steps taken to decrease patient anxiety before a physical exam should be utilized before any photos are taken.

CONCLUSION

Although newer diagnostic modalities such as modern ultrasonography and digital reconstruction CT and MRI have made the history and physical exam seem less important than they once were, they are still an essential part of patient care, especially in pediatric urology. In fact, most treatments in pediatric urology are not based on abnormal radiographic findings, but on history and physical exam findings. Common diagnoses such as nocturnal enuresis, inguinal hernia, and hypospadias all rely on the history and physical exam for determining treatment options and seldom require any imaging. Although at times the pediatric history and physical exam may seem daunting to the physician in training or a non–pediatric urology provider, with time and patience one can master these skills and thus provide exceptional care to these children.

BIBLIOGRAPHY

Agrawal AM, Tripathi PS, Shankhwar A, Naveen C: Role of ultrasound with color Doppler in acute scrotum management. J Fam Med Prim Care 2014;3(4):409–412.

Alkaram A, McCullough A: Varicocele and its effect on testosterone: Implications for the adolescent. Transl Androl Urol 2014;3(4):413–417.

Arfeen S, Rosborough D, Luger AM, Nolph KD: Familial unilateral renal agenesis and focal and segmental glomerulosclerosis. Am J Kidney Dis 1993;21(6):663–668.

Camurdan AD, Oz MO, Ilhan MN: Current stretched penile length: Cross-sectional study of 1040 healthy Turkish children aged 0 to 5 years. Urology 2007;70(3):572–575.

Chiocca E: The pediatric physical examination. In: Chiocca E (ed): Advanced Pediatric Assessment. Lippincott Williams & Wilkins, 2010, Chapter 8, pp. 147–150.

Chiocca E: The pediatric physical examination. In: Chiocca E (ed): Advanced Pediatric Assessment. Lippincott Williams & Wilkins, 2010a, Chapter 8, pp. 138–159.

Eccles MR, Bailey RR, Abbott GD, Sullivan MJ: Unravelling the genetics of vesicoureteric reflux: A common familial disorder. Hum Mol Genet 1996;5:1425–1429.

Esposito F, Di Serafino M, Mercogliano C, et al: The "whirlpool sign," a US finding in partial torsion of the spermatic cord: 4 cases. J Ultrasound 2014;17(4):313–315.

Garrett JE, Cartwright PC, Snow BW, Coffin CM: Cystic testicular lesions in the pediatric population. J Urol 2000;163(3):928–936.

Goede, J, Hack WM, Sijstermans, K, et al: Normative Values for Testicular Volume Measured by Ultrasonography in a Normal Population from Infancy to Adolescence. LUMC University Hospital Leiden, Leiden, The Netherlands, 2016. (Available online at: www.karger.com/hrp.)

Herold R, Beaver K (eds): The Practical Guide to HIPAA Privacy and Security Compliance. 2nd ed. CRC Press, 2014.

Hockenberry MJ, Wilson D, Winkelstein ML (eds): Wong's Essentials of Pediatric Nursing. 7th ed. Elsevier Mosby, St. Louis, 2005, pp. 133–134.

Hodhod A, Capolicchio JP, Jednak R, El-Sherbiny M: Testicular hypertrophy as a predictor for contralateral monorchism: Retrospective review of prospectively recorded data. J Pediatr Urol 2016; 12(1):34.

Homayoon K, Suhre CD, Steinhardt GF: Epididymal cysts in children: Natural history. J Urol 2004;171(3):1274–1276.

Kohelet D, Arbel E: A prospective search for urinary tract abnormalities in infants with isolated preauricular tags. Pediatrics 2000; 105(5):E61.

McPherson E: Renal anomalies in families of individuals with congenital solitary kidney. Genet Med 2007;9(5):298–302.

Murugasu B, Cole BR, Hawkins EP, et al: Familial renal adysplasia. Am J Kidney Dis 1991;18(4):490–494.

Shahid SK: Phimosis in children. ISRN (International Scholarly Research Notices) Urol 2012;2012:707329.

Singh H, Thomas EJ, Wilson L, et al: Errors of diagnosis in pediatric practice: A multisite survey. Pediatrics 2010;126(1):70–79.

Solorio MR: Health care of the adolescent. In: Taylor R (ed): Family Medicine: Principles and Practice. Springer Science & Business Media, 2002, pp. 212–214.

Son HS, Lee YS, Im YJ, et al: Can hypertrophy of the contralateral testis predict the absence of a viable testis in infancy with cryptorchidism: A prospective analysis. PLoS ONE 2016;11(3): e0151528.

Sy C, Nyame V, Haridas A: Sacral dimple—the role and yield of imaging. Austin Neurosurg Open Access 2014;1(4):1016.

Valerie E, Gilchrist BF, Frischer J: Diagnosis and treatment of urethral prolapse in children. Urology 1999;54(6):1082–1084.

Wani SA, Mufti GN, Bhat NA, et al: Ultrasonography: A useful diagnostic adjuvant in equivocal inguinal hernia on history. BAOJ Surg 2015;2(2):1–3.

Wilson JM, Aaronson DS, Schrader R, Baskin LS: Hydrocele in the pediatric patient: Inguinal or scrotal approach? J Urol 2008;180 (4 Suppl):1724–1727.

This page intentionally left blank

Introduction to Clinical Research Design

48

June M. Chan, ScD; David Tat, DO; & Stacey Kenfield, ScD

INTRODUCTION

What is a clinical trial? A **clinical trial** is a type of research study designed to evaluate the effect of an intervention on a health-related outcome in humans. The intervention can take many forms—medical therapies, behavior changes, or educational materials or websites. The outcome of interest can also be defined in a wide variety of ways—overall survival, disease progression, a body measure (eg, cholesterol level, weight), quality of life or well-being, behavioral change, or other factors. Clinical trials are done to evaluate new approaches to prevention, screening, diagnosis, or treatment.

There are many steps and components to ensure that such research is conducted rigorously, methodically, and in a logical fashion. This chapter briefly summarizes the following topics, as they relate to clinical trials: design, ethics, trial phases, strengths and weaknesses, and interpretation caveats. This chapter provides only a brief introduction to important concepts about understanding clinical trials and is meant to facilitate critical reading of the peer-reviewed literature. If you are planning to conduct clinical research or a clinical trial, we recommend that you seek out expertise from an epidemiologist or biostatistician, or pursue further in-depth education.

DIFFERENCES BETWEEN A CLINICAL TRIAL AND OTHER RESEARCH STUDIES

To better understand the design of a clinical trial, it is important to see how it fits into the context of other clinical epidemiology and research designs. There are many types of clinical research studies and different ways to categorize them. Four common designs are ecological studies, case–control studies, cohort studies, and clinical trials. To appreciate the pros and cons of a clinical trial, it is helpful to understand a little about the other types of study designs (see Figure 48–1).

Clinical Trials versus Other Epidemiologic Study Designs

What is the goal of epidemiologic studies? In general, the goal of epidemiologic research is to make causal inferences about what causes particular diseases or conditions in a given population. Several types of study designs are used for this purpose, each with strengths and weaknesses. We will summarize these briefly to understand better where clinical trials fit into the epidemiology toolbox, and how they have unique strengths and weaknesses.

First, there are some important concepts to understand when assessing a study design's rigor: outcome, exposure, temporality and causation, confounding, and bias.

A. Outcome

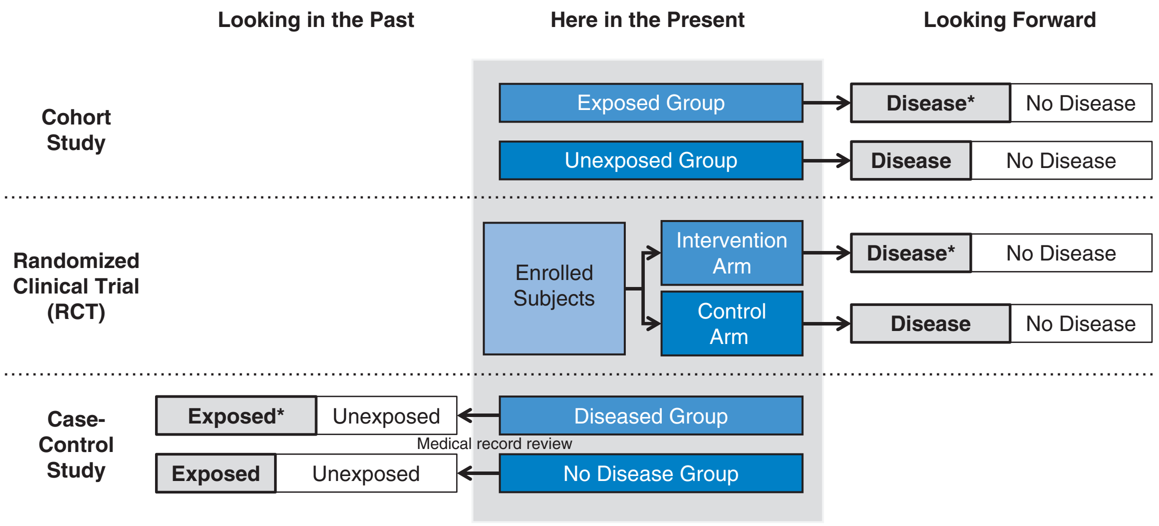
An **outcome** is typically the disease or condition that we are interested in understanding. For example, this could be heart attacks, cancer, diabetes, or urinary tract infections. There are also different ways to measure disease outcomes. One can simply look at whether people developed the disease (yes or no) during a certain time period. Alternatively, one could measure the rate of how frequently the disease occurred over a specific time interval (eg, cancer incidence rates are often presented as cases per 100,000 people per year).

B. Exposure

An **exposure**, in epidemiology, is what we think may be causing disease. We want to measure and assess the exposure in the population and see if we can link it to the outcome of interest. An exposure can include factors such as weight, diet, exercise, a drug, or environmental pollution.

C. Temporality and Causation

As one is trying to identify which exposures cause disease, there's a basic principle that the exposure comes *before* the



Study designs can be distinguished by comparing groups of participating patients, temporal relationships, and observational direction (into the past—retrospective—or the future—prospective).

*Represented proportions of disease/no disease or exposed/unexposed in this figure reflect examples of alternative hypotheses often examined in such studies

▲ **Figure 48–1.** Common epidemiologic study designs.

disease outcome—in other words, the cause comes before the effect. Therefore, a more rigorous design assesses exposures prior to the outcome occurring.

D. Bias

In epidemiology, **bias** is something that leads to a systematic error. Two major categories of bias in epidemiology are selection bias and measurement bias. **Selection bias** relates to the way a study population is identified, enrolled, or addressed. **Measurement bias** refers to errors in the way the exposures or outcomes are assessed. These terms will be defined further below within the explanations of specific study designs. Bias can occur in observational and interventional epidemiologic studies, including randomized controlled trials (RCTs).

E. Confounding

Confounding is a type of Bias. In a general sense, **confounding** means that something is confusing. In epidemiology, confounding is a technical term referring to a specific set of circumstances that limit our ability to make causal inferences. It refers to when there is a third factor confusing the ability to assess whether an exposure of interest is potentially causally related to the outcome of interest. This third factor creates confusion because it is a common cause of both the exposure of interest and the outcome. For example, if one is trying to study the link between exercise and prostate cancer death in men diagnosed with prostate cancer, smoking would be a potential confounding factor because it is likely inversely correlated with the exposure (exercise) and is positively associated with the outcome (prostate cancer death).

It is important to also realize that there are both known and unknown confounding factors. Thus, we can only speculate on what may be confounding the exposure–disease relationship of interest to the extent that we understand what things are associated with the disease. If we have limited understanding of the etiology of a condition, then we will also not be able to anticipate fully all confounding factors and account for them. Epidemiologic observational studies are susceptible to confounding, and investigators can address this in different ways, at either the design or analysis stage of the study. Further discussion of how to minimize confounding in epidemiology is beyond the scope of this chapter, but it is an important concept to understand when interpreting clinical research results and assessing the rigor of clinical trials.

▶ Observational Study Designs

A. Ecological Studies

This is a type of observational study where the investigator examines different forms of group-level data rather than individual-level data. For example, one could compare the estimated per capita intake of fat and the rates of cancer deaths for different countries as shown in Figure 48–2. This type of study can provide provocative initial results that are useful for hypothesis generating.

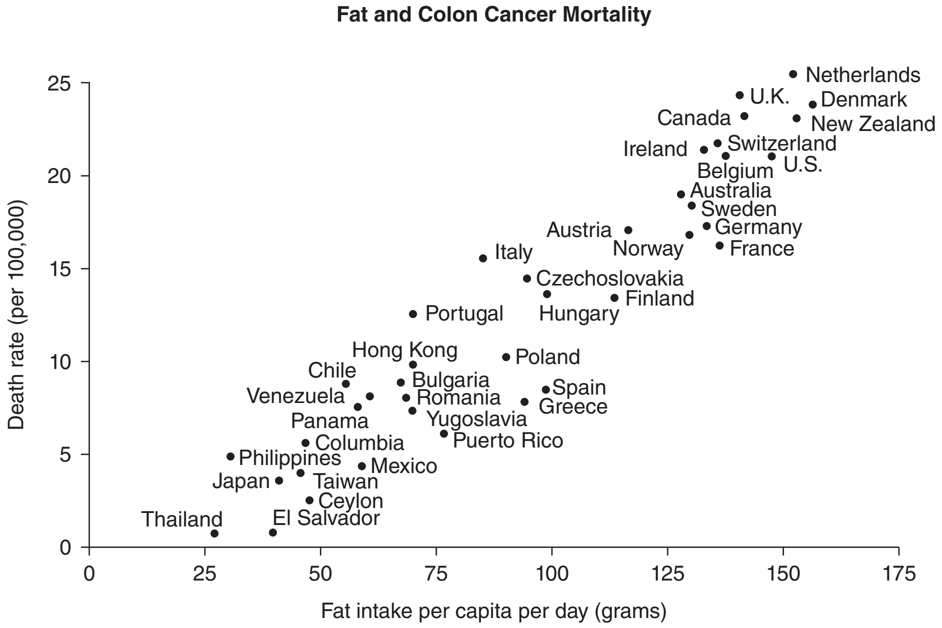
What are drawbacks of an ecological study? One of the major limitations is that it links together two group-level phenomena: per capita fat intake for a country and cancer death rates. These studies are not measuring what an individual actually eats and linking it to that specific individual's cancer outcomes. Rather, one collects data on estimated fat intake per person by assessing grossly how much fat is produced in the country's food supply, then divides that total by the country's population. In addition to not considering individual-level intake, the study does not consider food waste. This type of study also does not address the possibility that the "fat intake" may not be the real culprit, but highly correlated with something else that is truly causing the cancer deaths such as not eating enough vegetables (ie, vegetable intake is a confounding factor that is not considered).

B. Case–Control Study

In a case–control study, one collects individual-level data from two groups: those who have developed the disease or outcome of interest and those who have not. In this type of study, one looks backward in time (either through interviews, surveys, or accessing data collected historically, like a medical chart) and tries to identify what exposures may have differed between those who developed the disease (cases) versus those who did not (controls) (Figure 48–1). One could address questions such as "What is the association between statin use and cancer occurrence?" One could identify individuals who were diagnosed with cancer between 2010 and 2015 from a hospital cancer registry, then identify individuals who came to that same hospital for outpatient primary care and who were not diagnosed with cancer. They could then look back at the medical charts for these individuals during the few years leading up to 2010 and try to assess usage of statins, and compare the proportion of people who were using statins among the cases and controls.

1. Advantages—What are the advantages of a case–control study over an ecological study? Primarily, case–control studies get closer to assessing the real exposures and outcomes of interest at the individual level. However, there are still several limitations in this study design, and it can be difficult to conduct a well-designed case–control study.

2. Challenges—What are challenges in a case–control study? One of the main challenges of a case–control study is appropriate selection of the controls. One could choose people who do not have the disease from anywhere; however, to make appropriate comparisons, one should choose controls from the population of people who gave rise to the cases. This facilitates the ability to hone in on what it is, in that



▲ **Figure 48–2.** Correlation between fat intake and cancer occurrence. (Reproduced with permission from Carroll KK: Experimental evidence of dietary factors and hormone-dependent cancers, Cancer Res. 1975 Nov;35(11 Pt. 2):3374–83.)

population or common environment, that led to some people developing the disease. For example, what would happen if one chose cases of cancer from a registry in Illinois (IL), and controls from an outpatient clinic in California (CA), and tried to examine whether a specific statin medication led to the cancer outcomes by reviewing the medical charts? What if the common insurance policies in CA routinely reimbursed for the statin of interest, but not others, while in IL, there was more variety in types of statins eligible for reimbursement by the common insurance companies? This different reimbursement structure could create a spurious association between the statin medication of interest and cancer outcome that has nothing to do with the true cause but is linked to where the cases and controls resided; this is a form of selection bias. Therefore, the goal with control selection is to choose representative individuals from the population that gave rise to the cases.

Another common challenge in case–control studies is the desire to assess exposures before the outcome happens. By definition, when a case–control study is initiated, the outcome has already happened. Thus, to go back and try to assess the exposure status before the disease happened typically occurs in one of two ways; either one is examining previously assessed and recorded data (eg, medical charts), or one is interviewing or surveying the individuals and asking them to recollect what happened before their diagnoses. A limitation of the former approach is that one can only study things that have been recorded historically. This may work well for going through medical charts and obtaining information on weight, a clinical procedure, or medication usage. However, this approach does not work well for studying exposures such as diet or exercise, which are not routinely collected in a prospective fashion outside of a research study. The second approach, conducting surveys or interviews, can be used to collect data on behavior habits such as diet or exercise; however, in the case–control setting this will be subject to a type of measurement bias known as **recall bias**. This refers to the likelihood that someone with a disease may recall her/his past behaviors differently from someone who does not have the disease. Individuals with cancer may tend to overestimate their fat intake or sedentary habits because they subconsciously think that this led to their disease, whereas someone without cancer may be less likely to misreport.

3. Advantages—Typically, it takes less time (and sometimes money) to conduct a case–control study than a cohort study or RCT, and they do get one step closer to assessing individual-level data than an ecological study. Case–control studies are also well suited for assessing some genetic exposures, as germline genetics can be assessed using blood or saliva collected after a disease has already occurred, but still reflect the genetics of that individual before s/he developed the disease (because germline genetics are assumed to not change over time). Case–control studies can be conducted using entirely historically and routinely collected data, in which case, individual participants may not need to provide additional data for the study, potentially saving time and cost. However, if survey data or a blood sample is collected, then participants will be actively contacted, increasing time and costs.

C. Cohort Study

A typical cohort study identifies and consents a population, collects a large amount of potential exposure and confounding data on that group, and then follows these people over time to see who develops different diseases (Figure 48–1).

What are the strengths and weaknesses of a cohort study? In a cohort study, a strength is that many different diseases and exposures can be studied. Because of the way data are collected, exposures typically precede the outcome, so concerns regarding temporality and recall bias are limited. Additionally, there is an opportunity to collect a lot of detailed data upfront on exposures, confounding factors, and outcomes, and one is not restricted to preexisting information in historical records. While rigorous in design and useful for addressing many epidemiologic questions, limitations of cohort studies are that they often take a long time (decades) and are very expensive to initiate and maintain. They are also still subject to confounding and measurement error.

D. Clinical Trials

As mentioned above, a **clinical trial** is a type of research study designed to evaluate the effect of an intervention on a health-related outcome in humans. By virtue of having an "intervention," it is distinct from an "observational" study. The intervention could be a drug, surgical technique, educational tool, encouragement of a specific diet or exercise plan, psychosocial support, and so on. Similarly, the outcome can be a disease, health condition, behavioral change, and quality of life metric among other measures. Clinical trials are done to evaluate new approaches to prevention, screening, diagnosis, or treatment. There are several possible components of a clinical trial that also define their strengths and weaknesses, and these are discussed briefly below:

1. Comparison group—A clinical trial may or may not employ a comparison group. For example, one may conduct a single-arm trial to examine the question of whether providing a daily 1000-IU vitamin D supplement leads to increased blood levels of vitamin D after 12 weeks. The investigators may assess the blood levels in the population before and after the intervention. This can be done with or without a comparison group. If it is done without a comparison group, there is the limitation that an increase in blood level vitamin D due to other factors is not being rigorously controlled. For example, what if the study were conducted between May and July in a Northeastern state where sunlight exposure changes dramatically during this time? It is possible that circulating blood levels of vitamin D increase in general in the population due to the external factor of increased sunlight exposure, and not due to the supplement necessarily. In this instance, it would be important to have a comparison group that is tracked during the same time interval and that is *not* provided with the vitamin D supplement; their vitamin D levels at 0 and 12 weeks would be used to inform on background changes in the population and allow the investigators to hone in on the changes due to the supplement alone. Clinical trials without a comparison group are often done during pilot phases of research, to establish feasibility or acceptance or safety, and are often followed up by more rigorous designs.

2. Randomization—In a **randomized controlled trial (RCT)**, the decision of who is assigned to the intervention (ie, exposure) or usual care (control arm) is done randomly. Why is this helpful? The main benefit of this is that it can potentially minimize confounding by both known and unknown factors. This is one of the major advantages of a RCT over a cohort or other observational study design. How does the randomization minimize confounding? Mathematically speaking, if assignment to the intervention is done randomly, there should be no association between the intervention and other factors—thus, a factor that may have been a "common cause" of the exposure and outcome is now no longer associated with the exposure of interest (or intervention). It is important, at the analysis phase, that one checks whether there is confounding by suspected confounding factors, even in a RCT. Because of chance, particularly when there are small numbers, it is possible that the randomization plan will not adequately address confounding—so please check.

3. Masking—This was formerly referred to as "blinding." In some RCTs, the investigator can try to "mask" the participant or members of the study team to the random assignment of study participants to the intervention or control group. In a classic RCT example, investigators may be studying the effect of a drug that comes in pill form, and they can randomly ask the participants to take either the drug or a placebo that is manufactured to look, taste, and smell just like the real drug pill. In this instance, the participants are being masked to their assignments. Why is this helpful? If the participant or her/his managing physician is unaware as to which group the participant is assigned, this minimizes the chance that the participant or the physician may report on signs or symptoms of the disease or possible side effects in a biased way. For example, if the participant is not masked and knows that s/he is on the drug intervention, perhaps s/he will downplay any small symptoms, or postpone going to the physician for follow-up treatment because s/he believes that the drug is working. In contrast, one can easily imagine the opposite occurring among participants who know they have not received the drug intervention. These individuals may be more likely to report to the physician for further follow-up at early development of symptoms. Similarly, physicians may request more lab tests or imaging for a participant in a control group versus intervention group because they are more concerned about disease occurrence or progression in the untreated group. Thus, it is often important to try to mask both participants and their physicians to treatment assignment in RCTs. There is also a third level of masking that commonly occurs, whereby the statistician who analyzes the data can conduct the analysis by comparing two groups (A vs B), without knowing which group actually received the treatment or placebo. Other scientific investigators on the trial are also typically "masked" whenever possible.

4. Follow-up—Follow-up refers to observing participants over time and assessing the development of the outcomes of interest. In RCTs, it is important to try to have complete follow-up and minimize losses to follow-up or having participants go missing. This means that all participants enrolled and randomized are tracked and followed to see who develops the outcome and who does not, over the follow-up interval. If participants cannot be observed, then we have an incomplete picture of who develops the outcomes and who does not. In some situations, if the reason for the losses to follow-up are related to the exposure of interest (intervention) or to the outcome of interest, then study results could become biased. Therefore, it is particularly important to develop study procedures that allow the investigator team to keep track of study participants and assess them periodically for the development of the diseases or outcomes of interest. When a study experiences losses to follow-up, it is good practice to examine the baseline characteristics of those who stay in the study, and those who drop out or become lost to follow-up, as a way to explore if these participants differed in some way. A more rigorous clinical trial will have a control group, randomization, multilevel (participant, statistician/other investigators, treatment administrator) masking, and minimal losses to follow-up.

E. Randomized Controlled Trials (RCTs)

This design is distinct from the three observational study designs described above in that a RCT is intended to mimic a controlled experiment with an intervention. Rather than just observing a population or assessing life as it happens, a RCT typically involves actively administering some form of intervention (drug, educational tool, food supplement, etc) to one group and comparing outcomes in that group to another group that is managed with "usual care" (Figure 47–1). There is a natural progression of evaluation of any new agent, device, or intervention and this is divided into "phases."

Clinical Trial Phases

There are generally five clinical trial phases. Imagine one is testing a new drug for cancer management. Usually, preclinical work is conducted first in cell-line and animal models, to observe and document how that drug works in other systems. This type of research is called **preclinical studies**. Scientists use cell-line and animal model systems to learn about the biological function of potential therapeutic agents, and under what conditions that agent may work best. Once there is compelling evidence from preclinical studies suggesting that an agent may offer benefit in a human disease, then, a series of clinical trials may be mapped out for evaluation in humans.

A. Phase 0

Does it work? First, a phase 0 trial may be done in a small number of people and at a low (subtherapeutic) dose, just to test whether the agent has the expected effects on biological pathways in humans. A phase 0 trial seeks to evaluate whether the agent has the pharmacokinetic effects in humans that one would expect, based on the evidence to date, likely from observational studies or preclinical models. A phase 0 trial is usually conducted in a small number (~10) of healthy volunteers.

B. Phase 1

Is it safe, and at which dose? A phase 1 trial is usually conducted in <100 people and is designed to test the safety of the drug, often at different doses. For example, different groups of participants in the study may be given different doses of the drug, spanning a range from low to high. Then, the participants are observed to determine what type of side effects they experience at the different doses. A phase 1 trial may be conducted in healthy volunteers, or in the population with the disease of interest. The goal of a phase 1 study is to check that the drug is safe, or that a particular dose of the drug is "safe" and ready to be evaluated further for efficacy. The goal is to identify the dose that appears to have the most biological effect or promise of biological impact, while also balancing side effects.

C. Phase 2

Is it better than what is available, and as safe as standard treatment? Next, a phase 2 trial may be conducted to evaluate the efficacy and safety profile of the agent in the target population. A phase 2 trial usually consists of a few hundred participants (≤300), and the outcome is some measure of the biological impact or potential for efficacy on the target disease. For example, the ultimate goal might be to test whether a drug prevents prostate cancer death in individuals with localized prostate cancer. A phase 2 trial might evaluate the effect of the drug first on an early indicator of disease aggressiveness, such as PSA recurrence.

D. Phase 3: Scaleup

If a phase 2 trial indicates that the drug may have some therapeutic benefit in a small number of people with a certain disease, then a phase 3 trial is conducted to evaluate the agent more comprehensively for its efficacy, safety, and effectiveness. In a phase 3 trial, one would design a study that could observe an outcome such as prostate cancer death. Phase 3 studies are usually randomized. Phase 3 trials are conducted on hundreds to thousands of individuals who have or are at risk for the disease of interest.

E. Phase 4: Long-Term Effects

A phase 4 clinical study is conducted after the drug or agent has already been approved for use by the general public, and it is conducted to observe the long-term effects of the therapy.

Difference between Efficacy and Effectiveness

As described above, RCTs may address questions of feasibility, safety, efficacy, and effectiveness. **Efficacy** is how well a therapy impacts biology or a disease under controlled, ideal conditions. **Effectiveness** evaluates how well a therapy performs in real-world settings. For example, imagine that one is studying whether vigorous aerobic exercise prevents cancer progression. One may observe that a supervised exercise prescription that is implemented at a gym, with a trainer, and among individuals who are highly motivated and adherent (eg, who show up for all their exercise sessions) has a biological benefit in deterring cancer progression, based on assessing changes in intermediate tumor markers, and therefore concludes that the exercise prescription is efficacious. A larger RCT with longer follow-up may ensue that randomly assigns individuals to receive either the exercise prescription or the usual care, and the intervention group is given educational guidance but asked to exercise independently, because the study is larger and longer and needs to accommodate more people. The results of this trial may be very different and maybe no benefits are observed. Does this mean that the first study was wrong? Not necessarily—it could be that the participants in the second study did not execute the prescribed exercise with the same rigor, intensity, or duration as was experienced in the more controlled supervised setting, and therefore one might conclude that while the exercise prescription had efficacy, the provision of the exercise prescription and education was not effective.

Intention to Treat

In a randomized controlled trial, it is important to conduct the main analyses following the "intention to treat" principle. This means that the study population should be analyzed in terms of their original randomization assignment and not according to what they actually do. The mnemonic to help remember this is: "once randomized, always analyzed." This maintains the masking and randomization features of the study design, and thereby minimizes bias and confounding. For example, if a participant is randomized to placebo in a study examining the effects of aspirin on cancer incidence versus placebo, but medical chart review during the trial shows that by chance the participant took aspirin regularly, that participant should still be analyzed as assigned to placebo.

INTERPRETATION CAVEATS FOR RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials have several advantages over cohort and case–control studies. When conducted well, they should minimize the potential for recall bias and confounding, and the cause (the intervention or exposure) definitely precedes effect (outcome). RCTs are often considered a gold standard for informing the evidence based on causal relationships between exposures and outcomes. However, there are several key limitations about RCTs that are important to consider and appreciate when planning a study and interpreting results, either within one study or across studies. RCTs often require a considerable amount of logistical management, time, and money. Some drawbacks of RCTs that are less often appreciated are limitations related to dose, duration, timing, and ethics. These are each addressed briefly below.

Dosage

As RCTs are mimicking a controlled experiment, they typically administer only one level of the intervention at a time. The prescription for the intervention is specific; for example, 1000 IU vitamin D pills given orally per day, or aerobic exercise recommended for 30 minutes, 3 days per week. Occasionally, a trial may accommodate a few interventions simultaneously, but this usually requires the addition of more arms or groups to the trial, and increases the sample size and level of complexity. This means that one cannot study the full range of the exposure and needs to be fairly confident that the dose selected is biologically meaningful in that population for that outcome, before starting the study. Hence, the phases of clinical trials discussed above are all focused on fine-tuning these characterizations about the dose of the intervention in a methodical and incremental way, before launching a full-scale phase 3 trial. In contrast, observational studies are often useful for examining the association between an exposure and an outcome across the spectrum of levels of that exposure. It is best if there are both observational cohort and early phase trial data available to inform on the best dose for a phase 3 trial. Even with proper preparatory work, the biologically relevant dose may be missed.

There are examples from the dietary supplement and cancer RCT literature whereby scientists observed an inverse association between a food and a cancer outcome, then tried to conduct a RCT based on selection of a particular nutrient or set of nutrients that were highly concentrated in those foods, and observed either null results or results that were even contrary to their original hypotheses.

Duration and Timing

Another caveat of RCTs is that they are labor-intensive and expensive to conduct and often cannot exactly mimic the circumstances under which a particular risk factor has been observed to be linked to a disease. For example, if we observe that a diet high in vegetables and fruit is inversely related to cancer outcomes in cohort studies, we may move on to conduct a RCT recommending five to seven vegetables or fruits per day in adults aged 60–75 years, for 5 years. Even if the data from the cohort studies are true, the RCT may not observe a beneficial effect in the short timeframe of 5 years, if in reality, it is a lifetime or decades of eating vegetables and fruits that protects older adults from cancer development. This may be a case where the duration of the intervention is too short to observe an effect.

In a similar fashion, there may be particular timepoints in the life course when the intervention is more impactful on the outcome of interest. For example, when considering the complex relationships between sex hormones and later development of cancer, exposures during puberty or in utero might be especially important for the development of cancer decades later. Thus, sometimes the appropriate timing of the intervention and follow-up will be infeasible within the RCT design. A related concept is the recognition that certain interventions work best during certain phases of the disease. For example, perhaps an intervention (eg, exercise) is especially helpful to prevent progression of a cancer (ie, exercise may stem angiogenesis or metastatic potential), rather than the development of the disease (eg, exercise might have a limited effect on initial DNA repair mechanisms critical to tumor inception). Thus, again, sometimes a risk factor has been identified from a cohort study over decades of follow-up, but cannot be replicated in a RCT because the timing of the delivery of the intervention is too late or too early, relative to the specific window of time when that disease is susceptible to that intervention.

Study Population

It is important to recognize that even the most well-designed and implemented RCT could still produce null or contrary results, even when the intervention is actually beneficial for the disease, if the study is conducted in the wrong population. As our understanding of disease heterogeneity, pharmacogenetics, and other host–environment interactions grows, it becomes increasingly apparent that medical approaches may need to be tailored or personalized to the individual's genetics, microbiome, nutritional levels, or other factors to really be impactful. For example, in the nutrition and cancer literature, there are examples where supplementation had a large impact in one population but not another, likely because the populations had different levels of dietary sufficiency at the beginning of the study (see "Learning Example" section below).

Adherence

While investigators assign participants to intervention or control groups in RCTs, individuals still make daily choices that may affect the full impact of that assignment. This refers to the adherence of the participants to their assignment. If people are given pills but do not take them, this is an example of lack of adherence. Similarly, if some individuals are assigned to a "usual care" arm in a study of exercise and cancer, but decide to start a new diet and exercise routine while in the study, this is also a form of lack of adherence. The control arm now contains individuals who are experiencing something similar to the intervention. Sometimes this is also referred to as "crossover." It is difficult to interpret the efficacy of the intervention if there is substantial lack of adherence noted in one or both of the randomized arms.

For example, in the prostate cancer arm of the Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO), 76,693 men were randomized to an intervention (annual PSA tests for 6 years and digital rectal examinations for 4 years) or control (usual care) group, to evaluate the outcome of prostate cancer mortality. At this time (1991–2001), rates of PSA testing were already quite high in standard patient management, with 44.1% of the control arm receiving at least one serum PSA test in the 3 years before randomization (Andriole et al, 2009). In 2009, the investigators reported that in the intervention arm, rates of compliance were 85% for PSA testing and 86% for digital rectal examination, while rates of screening in the control arm increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41% to 46% for digital rectal examination (Andriole et al, 2009). In an updated analysis, which extended mortality follow-up to a maximum of 19 years after randomization, it was estimated that 99% of the men in the intervention arm and 86% of the men in the control arm received any PSA testing during the trial. There were 255 deaths from prostate cancer in the intervention arm and 244 deaths from prostate cancer in the control arm, resulting in a rate ratio (RR) of 1.04 (95% confidence interval [CI], 0.87–1.24), suggesting that there was no benefit of organized versus opportunistic screening (a distinction only made in subsequent years to highlight the contamination issue) (Pinsky et al, 2017). Given that opportunistic screening was so high, it was ultimately impossible to see a benefit of annual screening compared to the control arm, although a true clinical benefit of screening may still exist compared to no screening. Published on the same day in the *New England Journal of Medicine* in 2009, the European Randomized Study of Screening for Prostate Cancer reported that PSA-based screening reduced the rate of death from prostate cancer by 20% comparing the screening to control groups, in a setting with different clinical management practices (Pinsky et al, 2017; Schroder et al, 2009).

ETHICAL CONSIDERATIONS

Equipoise

An important underlying principle about RCTs is that they should be conducted when we are at a stage of equipoise in our knowledge about the exposure–disease relationship. In a RCT, we are conducting a human experiment that could be invasive, labor-intensive, and burdensome, and we are *randomly* assigning populations to different management options. Therefore, the ability to *randomize* someone to a treatment is ethically grounded in the concept that our knowledge is in equipoise; we truly do not know whether the intervention is going to affect the outcome, and there is no evidence of superiority of one strategy over the other because data are equivocal. This means that there are data supporting varying outcomes—no effect, benefit, or possible risks.

Ethical Conduct of Clinical Research

In general, the risk–benefit tradeoffs of any clinical research should be assessed, and studies should be conducted only when the potential benefits outweigh the risks. When making these assessments, one considers the possible physical, psychological, social, and economic risks for the participant, as well as the potential benefits to the individual and society.

Given this, it should be recognized that there are certain scientific questions that are not amenable to RCT study designs because it would be inappropriate to randomly assign people to certain "exposures." For example, it would not be ethical to test whether cigarette smoking affects urinary tract infection risk by randomly assigning one group to smoke a pack a day versus not (ie, by assigning a control group to not smoke a pack a day). We cannot conduct RCTs on processed meat intake and risk of kidney stones, or alcohol and fertility, as it would be unethical to randomly assign some people to eat processed meat or drink alcohol (both are classified as carcinogens according to the International Agency for Research on Cancer). Thus, it should be recognized that in the larger picture of clinical research, there are certain questions that can be addressed only by observational studies, and there is an ongoing and important need for rigorously conducted cohort studies to support knowledge acquisition in these areas.

Clinical versus Statistical Significance

For *any* type of clinical research study (not just a RCT), it is very important to distinguish between clinical and statistical significance. **Clinical significance** refers to whether something has the potential to make a clinically meaningful difference, if the association is real. **Statistical significance** refers to *a priori* selected thresholds for making a type I error that the investigators choose for their study analysis. (*Note*: Type 1 error is when you reject the null hypothesis when it is true.) Results can be clinically significant but not statistically significant, or statistically significant but not clinically meaningful (see Table 48–1 for examples of each). However, often, researchers blur these concepts. It is a common oversight observed in all levels of clinical research, from early learners through experienced senior faculty, in peer-reviewed publications as well as presentations at professional conferences. Thus, beware when someone simply states that a result is "not significant." Ask, not significant on the basis of what? It is

Table 48–1. Examples of clinical and statistical significance.

Statistically significant	Clinically relevant: Yes	Clinically relevant: No
Yes	HR 0.37 (95% CI 0.22–0.66) for death for assignment to Mediterranean diet with nuts + having high baseline nut consumption versus assignment to control *and* rarely eating nuts at baseline, from the PREDIMED trial (Gausch-Ferre et al, 2013)	An example of "barely statistically significant" and a small/modest relative risk reduction is HR = 0.92 (95% CI 0.86–0.998) for multivitamins versus placebo and total cancer incidence in PHSII (Gaziano et al, 2012)
No	HR = 0.63 (95% CI, 0.39 to 1.02) for radical prostatectomy versus observation for outcome of death due to prostate cancer or treatment in PIVOT trial (Wilt et al, 2017)	HR = 1.02 (95% CI 0.94–1.10) for vitamin C supplementation versus placebo and risk of total cancer in PHSII (Wang et al, 2014)

critical that this be qualified by additional words or context to clarify whether this means not statistically significant or not clinically significant. This interpretation caveat is relevant for evaluating any clinical research result and is particularly important for RCTs because RCTs often drive changes in treatment, policy, and guidelines. Therefore, inappropriate overemphasis on statistical significance while ignoring or underemphasizing clinical significance can have large public health ramifications (see Table 48–1 for numeric examples). As you go through your career as a clinical research learner, educator, or practitioner, be wary, speak up, and promote precision in the language around "significance!"

A LEARNING EXAMPLE

For any clinical research question, regardless of the study design, it is useful to define the population, intervention (or exposure), control (or comparison) group, and outcome. Sometimes this is referred to by the acronym **PICO** (Schlosser et al, 2007). It is important to keep in mind that slight differences in how these basic components are defined can change the hypothesis being tested. Thus, trials that appear to be testing the same question may in fact be testing different questions and therefore may have different conclusions. As an example, consider the following three RCTs that all examined selenium or vitamin E supplementation and prevention of incident prostate cancer.

In 1996, the Nutritional Prevention of Cancer (NPC) trial reported that among 1312 individuals with a history of basal or squamous cell carcinoma, those who received 200 μg of supplemental selenium did not experience a lower risk of new skin cancers compared to those assigned to placebo (Clark et al, 1996). However, there was a clinically and statistically significant reduction in total cancer deaths (secondary outcome) in those assigned to selenium versus placebo (Hazard Ratio (HR) 0.61, 95% CI 0.46–0.82), and the trial was stopped. Among 927 men, the HR for prostate cancer was 0.35 (95% CI 0.18–0.65), suggesting a 65% reduction in the risk of incident prostate cancer in this population (Duffield-Lillico et al, 2003).

In 1998, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) conducted among 29,133 Finnish male smokers reported a *higher* occurrence of lung cancer (primary outcome) among those randomized to β-carotene (20 mg) versus placebo, and no association for α-tocopherol (50 mg) and lung cancer risk in its original report (ABCT, 1994). In secondary analyses, the study observed an ~36% lower incidence (95% CI from −56% to −6%) and approximately 40% lower mortality (95% CI from −65% to −1%) due to prostate cancer, among men randomized to α-tocopherol versus placebo (Heinonen et al, 1998).

On the basis of the results above and other corroborating findings, the Selenium Vitamin E and Prostate Cancer Prevention trial (SELECT) enrolled 35,533 American males and randomized them to either supplemental selenium (200 μg), vitamin E (400 IU), both, or placebo. The primary outcome of interest was incident or newly diagnosed prostate cancer, and men were excluded if they had a baseline PSA level of >4 ng/mL or a suspicious digital rectal exam. After approximately 5.5 years of median follow-up, the trial was stopped because of the results from a formal interim analysis that indicated convincing lack of evidence of benefit for either supplement, and no possibility of benefit within the planned follow-up time (Lippman et al, 2009) (see Table 48–2 for further details).

What might be reasons for these apparently discrepant results? There are a few points to note:

- **Population**: The study populations of NPC and SELECT were different with regard to the baseline selenium level, as the NPC was planned in a geographic region known to have low selenium levels. With further follow-up and analyses, the apparent reduction in risk of prostate cancer in NPC appeared to be limited to those with a baseline circulating selenium level in the lowest two tertiles (<123.2 ng/mL) (Duffield-Lillico et al, 2003), whereas the baseline circulating level of selenium among SELECT men was ~136 μg/L. With further follow-up, SELECT investigators reported that selenium supplementation actually *increased* the risk of high-grade prostate cancer among those with high-baseline toenail selenium (HR = 1.91, 95% CI 1.20–3.05) and did not increase risk among those with lower baseline levels (Kristal et al, 2014). The formulations of selenium used in each trial were also different.

Table 48–2. Three RCTs addressing the question of vitamin E or selenium supplementation and risk of prostate cancer.

Parameter	NPC (1998)[a]	ATBC (1998)[b]	SELECT (2009)[c]
Population: Who was in the study population? How does the study population compare to the general population? Be specific!	1312 individuals aged 18–80 years, with history of basal or squamous cell carcinoma; 5-year life expectancy; no other malignancies diagnosed in past 5 years, and who lived in regions with low selenium soil levels (~75% enrolled were male)	29,133 Finnish male smokers (5+ cigarettes/day), aged 50–69 years, with no prior cancer, and not already taking vitamin E, vitamin A, or β-carotene supplement.	35,533 healthy men with PSA ≤ 4 ng/mL, negative DRE, age 50+ years for black men or 55+ for other men, living in USA, Canada, or Puerto Rico
Randomization: Was it randomized?	Yes	Yes	Yes
Intervention: What was the intervention or exposure?	200 μg supplied as 0.5-g high-selenium brewer's yeast tablet	*dl*-α-Tocopherol acetate 50 mg (vitamin E) *or* 20 mg β-carotene	200 μg/*dl*-selenomethionine) *or* vitamin E (400 IU/day of all *rac*-tocopheryl acetate
Control (or comparison): What was the reference (or control) group?	Placebo	Placebo	Placebo
Outcome: What was the primary outcome? What were secondary outcomes?	1° new basal or squamous cell skin cancer 2° total and cancer-specific mortality; incidence of lung, colorectal, and prostate cancer (added in 1990)	1° lung cancer incidence 2° other cancer incidence	1° prostate cancer incidence 2° lung and colorectal cancer incidence, other cancers, total mortality
Follow- up: How complete was follow-up? Were losses to follow-up associated with the intervention?	No loss to vital status follow-up; 0.6% (*N* ~ 9) did not provide further medical follow-up	No loss to follow-up	~5% (loss to follow-up defined as having a last-contact date >24 months before analysis)
Masking: Was there masking? If so, how many levels?	Triple-masked (patient, physician, statistician)	Triple-masked	Triple-masked
Adherence: Did study participants follow their random assignments? Was there "crossover"?	82% of participants missed taking a pill <2 times/month	80% of participants took >95% of capsules (based on residual capsule counts)	83% at end of year 1; 65% at year 5
Intention to treat: Was the primary analysis done as intention to treat?	Yes	Yes	Yes
Calendar year/timing	1983–1993	1985–1993	2001–2008
Results	BCC, relative risk (RR) 1.10 (95% CI 0.95–1.28) SCC, RR 1.14 (95% CI 0.93–1.39) Total mortality, RR 0.83 (95% CI0.63–1.08) Total cancer mortality, RR 0.50 (0.31–0.80) Total cancer incidence, RR 0.63 (95% CI 0.47–0.85) Prostate cancer incidence, RR 0.51 (95% CI 0.29–0.87)	Change in Incidence for vitamin E versus placebo: Lung: 2% (95% CI = from 14% to 12%) Prostate: 32% (95% CI = from 47% to –12%)	HRs for prostate cancer, compared to placebo: Vitamin E: 1.13 (99% CI, 0.95–1.35) Selenium: 1.04 (99% CI, 0.87–1.24) Vitamin E + selenium: 1.05 (99% CI, 0.88–1.25) No statistically significant differences for any pre-specified secondary cancer endpoints

[a] **NPC:** Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, et al: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 1996;276(24):1957–1963.

Duffield-Lillico AJ, Dalkin BL, Reid ME, Turnbull BW, Slate EH, Jacobs ET, et al: Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: An analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 2003;91(7):608–612.

[b] **ATBC:** The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. New Engl J Med. 1994;330:1029–1035.

Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, et al: Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst 1998;90(6):440–446.

[c] **SELECT:** Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301(1):39–51.

- **Intervention**: The dosage of β-carotene provided in ATBC was different from that in SELECT.
- **Outcome**: Importantly, the diagnosis and hence the type of prostate cancer identified in each study was likely different, as prostate cancer was not a primary outcome of the NPC or ATBC trials. While participants had to be free of a history of cancer malignancy to enter those trials, they were not actively *screened* for prostate cancer as part of the eligibility assessment. In contrast, to be eligible for SELECT, participants were screened and had to be PSA- and DRE-negative. Prostate cancer is a heterogeneous disease, known to have both indolent and aggressive phenotypes. The NPC and ATBC trials began before PSA screening became common, and in ATBC, approximately 44% of the incident cases were stage III or IV. SELECT screened out individuals with prevalent prostate cancer at the start of the trial, and most of the incident cases occurring during the trial were early-stage, PSA-detected, grade ≤3 + 4. Thus, it is possible that ATBC and NPC were in fact testing the effect of each supplement on the *progression* of presymptomatic cancer, whereas SELECT was really testing the effect on primary prevention.

CONCLUSIONS

In conclusion, clinical trials are one of several types of study designs available for clinical and epidemiologic research. A randomized controlled trial (RCT) is one specific type of clinical trial, which is often considered the gold standard for making causal inferences. However, RCTs have important limitations that should be considered when choosing a study design or interpreting results.

ACKNOWLEDGMENTS

JMC acknowledges Graham Colditz for being the first person to teach her to look out for many of the RCT interpretation caveats described and discussed in this chapter.

BIBLIOGRAPHY

ABCT (The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group): The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. New Engl J Med 1994;330:1029–1035.

Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al: Mortality results from a randomized prostate-cancer screening trial. New Engl J Med 2009;360(13):1310–1319.

Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, et al: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 1996; 276(24):1957–1963.

Duffield-Lillico AJ, Dalkin BL, Reid ME, Turnbull BW, Slate EH, Jacobs ET, et al: Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: An analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 2003;91(7):608–612.

Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, et al: Multivitamins in the prevention of cancer in men: The Physicians' Health Study II randomized controlled trial. JAMA 2012;308(18):1871–1880.

Guasch-Ferre M, Bullo M, Martinez-Gonzalez MA, Ros E, Corella D, Estruch R, et al: Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med 2013;11:164.

Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, et al: Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: Incidence and mortality in a controlled trial. J Natl Cancer Inst 1998;90(6):440–446.

Kristal AR, Darke AK, Morris JS, Tangen CM, Goodman PJ, Thompson IM, et al: Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk. J Natl Cancer Inst 2014;106(3):djt456.

Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al: Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301(1):39–51.

Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, et al: Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123(4):592–599.

Schlosser RW, Koul R, Costello J: Asking well-built questions for evidence-based practice in augmentative and alternative communication. J Commun Disord 2007;40(3):225–238.

Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al: Screening and prostate-cancer mortality in a randomized European study. New Engl J Med 2009;360(13):1320–1328.

Wang L, Sesso HD, Glynn RJ, Christen WG, Bubes V, Manson JE, et al: Vitamin E and C supplementation and risk of cancer in men: Posttrial follow-up in the Physicians' Health Study II randomized trial. Am J Clin Nutr 2014;100(3):915–923.

Wilt T, Jones K, Barry M, Andriole G, Culkin D, Wheeler T, et al: Radical prostatectomy versus observation for early prostate cancer: Follow-up results of the prostate Cancer Intervention versus Observation Trial (PIVOT). J Urol 2017;197(4 Suppl):e915.

This page intentionally left blank

Index

Note: Page numbers followed by *f* and *t* denotes figure and table repectively.

A

Abdominal leak point pressure (ALPP), 494, 503
Abscesses
  paranephric, 212
  perinephric, 212
  prostate, 219, 220*f*
  renal, 212, 213*f*, 334
Absorptive hypercalciuric nephrolithiasis, 263
Acetate, 360
Acetohydroxamic acid, for calculi prevention, 285
Acetowhite areas, 253
Actinomycosis, 235
Active surveillance, 366
Activin, 705
Acucise endopyelotomy, 144
Acute kidney injury (AKI), 551
  causes of, 551, 552*t*
  intrarenal causes of, 553
    laboratory findings, 553–554
    symptoms and signs, 553
    treatment, 554–555
  nonspecific intrarenal causes of, 554–555
    laboratory findings, 554–555
    prognosis, 555
    symptoms and signs, 554–555
    treatment, 554–555
  postrenal, 555
  prerenal, 551
    causes, 551
    laboratory findings, 552
    symptoms and signs, 551
    treatment, 552–553
  vascular causes of, 553
Acute pyelonephritis
  definition, 209
  management, 209–210
  presentation and findings, 209
  radiographic imaging, 209, 210*f*
Acute urinary retention, 37
Adaptive immunity, 415
Adenocarcinoma
  of bladder, 311–312
  of kidney (*See* Renal cell carcinoma [RCC])
  laparoscopic treatment of, 514
  of urachus, 586, 587*f*
Adenomatoid tumors, of epididymis, 385
Adjuvant therapy
  criteria for, 408
  systemic therapy as, 408
Adrenal adenoma, 514
Adrenal gland
  anatomy, 1
  blood supply, 1
  computed tomography of, 87*f*
  disorders of, 509–519, 510*f*
    androgenic syndromes, 515–516
    Cushing's syndrome, 510–515
    incidentaloma, 509–510
  histology, 1
  lymphatic vessels, 1
  relation of, to other organs, 1, 3*f*
Adrenalectomy, laparoscopic, 162–163, 163*f*
Adrenergic receptors, in micturition, 460–462
β_3-Adrenoceptor agonists, 479
Adrenocortical tumors, 516
Adrenocorticotropic hormone (ACTH)
  description of, 511
  overproduction of (*See* Cushing's syndrome)
Adult polycystic kidney disease, 522*f*, 522–525, 524*f*
  complications, 525
    infection of cysts, 525
    pyelonephritis, 525
  differential diagnosis, 523
  etiology and pathogenesis, 522
  imaging findings, 523
  instrumental examination, 523
  laboratory findings, 523
  pathology, 522*f*, 522–523
  prognosis, 525
  signs and symptoms, 523
  treatment, 525
Afferent pathways, micturition, 454
Agenesis, of seminal vesicle, 600
Aging
  androgen deficiency in (*See* Androgen deficiency)
  birth defects/disease in offspring, 738
  erectile dysfunction and, 611
  fertility affected by, 737
  genetic disorders and, 738*t*
    sperm chromosomal anomalies, 737–738
    sperm genetic mutations, 738
  spermatogenesis affected by
    semen quality, 737
    sperm production, 737, 737*t*
  testis changes secondary to
    Leydig cells, 735
    Sertoli cells, 736
    testosterone, 735–736, 736*f*
AIDS. *See* HIV/AIDS
Alcohol, and erectile dysfunction, 611
Aldosterone, 517
Aldosteronoma, 517
Allogeneic vaccines, 417
Allopurinol, for calculi prevention, 285
Alpha-fetoprotein (AFP), 380
Alprostadil, for ED, 619–620
Alzheimer disease, 474
American Society for Therapeutic Radiology and Oncology (ASTRO), 369
American Urological Association (AUA), 594
American Urological Association Symptom Index, 107–108
Amiloride, 519

Aminoglycosides, for urinary tract infection, 208
Analgesic nephropathy, 546
Andriol, 617
Androderm, 616
AndroGel, 616
Androgen ablation therapy, for prostate cancer, 370*t*
Androgen deficiency
  diagnosis of
    algorithm for, 740*f*
    laboratory findings, 740–741
    organ system effects of testosterone, 738–739, 739*t*
    patient history and examination, 739
    radiological testing, 741
  future treatments
    dehydroepiandrosterone, 744–745
    5α-dihydrotestosterone, 744
    human chorionic gonadotropin, 744
    17α-methyl-19-nortestosterone, 744
    selective androgen receptor modulators, 744
    selective estrogen receptor modulators, 744
  testosterone replacement therapy for
    contraindications and precautions, 743
    formulations, 741*t*, 741–742
    monitoring treatment, 743, 744*t*
    risks, 742–743
Androgens, 607
Aneurysms, renal artery
  description of, 531–532, 532*f*
  rupture of, 531–532
  transcatheter embolization of, 114
Angiography
  aortorenal and renal, 71, 74, 80*f*
  inferior venacavography and selective venography, 74, 80*f*–81*f*
  miscellaneous urologic, 74
Angiomyolipoma (AMLs)
  computed tomography of, 330*f*, 331
  definition of, 341
  diagnosis of, 341
  differential diagnosis of, 333–334
  incidence of, 341
  management of, 341–342
  transcatheter embolization for, 111, 111*f*
  treatment of, 342
  tuberous sclerosis and, 341
Angiotensin-converting enzyme (ACE) inhibitors, for IgA nephropathy, 543
Anorgasmia, 609
Anterior lateral thigh flap phallourethroplasty, 761*f*, 761–762, 764–766
Anterior urethral valves, 649
Antiandrogens, 611
Antibiotics
  pregnancy and, 222*t*
  urinary tract infection treated with, 205–209
Antibodies, 417
Anticholinergics
  neurogenic bladder treated with, 478–479
  urgency urinary incontinence treated with, 504–505
Antigen-presenting cell, 415
Antimuscarinics, in micturition, 459–460
Antineutrophil cytoplasmic antibody (ANCA) diseases, 541
Antioxidant therapy, for male infertility, 730
Antisperm antibodies (ASAs), 712
Antisperm antibody test, 712
Anuria, 37
Apenia, 645
Apomorphine, 619
Appendix testis torsion, 773–774
Aprepitant, 458
Arteriography, for erectile dysfunction evaluation, 614
Arteriovenous aneurysm, 533–534, 534*f*
Arteriovenous fistulas (AVFs), 533
  congenital, 107
  transcatheter embolization of, 107
Artificial urinary sphincter (AUS), 504
Asymptomatic bacteriuria
  in catheterized patients, 223
  description of, 478
Atrophic urethritis, 661–662
Atypical genitalia. *See also* Disorders of sex development (DSD)
  algorithm for initial workup of, 685*f*
  biochemical evaluation, 679, 683*f*
  chromosomal evaluation, 679
  diagnostic laparotomy/laparoscopy, 679, 683
  differential diagnosis, 686*t*
  history examination, 677
  physical examination, 677, 682*f*
  radiographic evaluation, 679, 684*f*
  sex assignment, 683, 685
Atypical small acinar proliferation (ASAP), 353
Autologous vaccinations, 417
Autonomic nervous system, 473
Autosomal dominant polycystic kidney disease, 547–548, 548*t*
Axitinib, 420
Azoospermia
  algorithm for evaluation of, 715*f*
  description of, 27, 713, 742

B

Bacillus Calmette–Guerin (BCG), 317–318, 416
Bacterial prostatitis
  acute, 217–218
  chronic, 218–219
Bacteriuria, 51
  bacterial cultures, 54–55
    cultures for tuberculosis, 55
  microscopic examination, 54
Balanoposthitis, 775
Balkan nephropathy, 321
Bardet–Biedl syndrome, 717
Bartholin's glands, 632
Beckwith–Wiedemann syndrome, 342–343
Benign prostatic hyperplasia (BPH), 593–599
  American Urological Association Symptom Index scores for, 107–108
  clinical findings
    cystoscopy, 596
    imaging, 596
    laboratory findings, 596
    other tests, 596
    signs, 594, 596
    symptoms, 594, 595*t*
  differential diagnosis, 596
  epidemiology, 593
  etiology, 593–594
  incidence, 593
  medical treatment of, 597*t*

    - alpha-blockers, 597, 597*t*
    - combination therapy, 597–598
    - phytotherapy, 598
    - 5α-reductase inhibitor, 597
  - pathology, 594
  - pathophysiology, 594
  - surgical treatment of
    - holmium laser enucleation of the prostate, 598
    - prostate artery embolization, 107–109, 109*f*
    - simple prostatectomy, 598–599
    - transcatheter embolization, 107–109, 109*f*
    - transurethral incision of the prostate, 598
    - transurethral microwave thermotherapy, 599
    - transurethral resection of the prostate, 108, 598
    - transurethral vaporization of the prostate, 598
  - testosterone therapy and, 743
  - watchful waiting for, 596–597
- Bevacizumab
  - metastatic renal cell carcinoma treated with, 340
  - toxicities of, 409*t*
- Bias, 782, 784
- Bicarbonate reabsorption defects, 549
- Bifid scrotum, 774
- Bifid ureter, 20
- Bilateral nodular hyperplasia, 518
- Bilharziasis. *See* Schistosomiasis
- Bimix, for ICI, 620
- Biothesiometry, 615
- Birt–Hogg–Dubé syndrome, 335, 341
- Bispecific T-cell engager (BiTE), 418
- Bladder
  - anatomy of, 7*f*, 8
  - appearance, 7–8
  - blood supply, 8
  - contractions of, 490
  - exstrophy of, 24
  - foreign body in, 589
  - histology, 8, 11*f*
  - lymphatics, 8
  - muscarinic receptors in, 478
  - nerve supply, 8
  - neurogenic (*See* Neurogenic bladder)
  - physical examination, 42
  - relation of, to other organs, 8, 9*f*, 10*f*, 11*f*
- Bladder calculi, 125, 285, 286*f*–287*f*
- Bladder cancer, 309
  - clinical findings
    - cystourethroscopy and tumor resection, 314–315
    - imaging tests, 313*f*, 313–314, 314*f*
    - laboratory findings, 313
    - signs, 313
    - symptoms, 312
  - histopathology
    - adenocarcinomas, 311–312
    - normal urothelium, 311, 312*f*
    - papilloma/PUNLMP, 311
    - rare epithelial and nonepithelial cancers, 312
    - squamous cell carcinoma, 312
    - transitional cell carcinoma, 311, 312*f*
    - undifferentiated carcinomas, 312
  - incidence, 309
  - localized, 419
  - metastatic, 412
  - multifocal, 126*f*
  - natural history and treatment selection, 315–317
  - pathogenesis, 309–310
  - radiotherapy, 319, 430–433
    - combined modality therapy, 431–432, 432*t*
    - EBRT management, 430–431
    - improving treatment outcomes, 432–433
    - toxicity, 433
  - risk factors, 309
  - staging, 310*f*, 310–311
  - treatment, 317–321
    - Bacillus Calmette–Guerin, 416
    - chemotherapy, 319–320
    - combination therapy, 320–321
    - intravesical chemotherapy, 317–318
    - radiotherapy, 319
    - surgery, 318–319
- Bladder contractility index (BCI), 492
- Bladder contractility nomogram, 492*f*
- Bladder disorders
  - acquired
    - diverticula, 590
    - interstitial cystitis/bladder pain syndrome, 587–589
    - pelvic lipomatosis, 592
    - vesical fistulas, 590–592, 591*f*
    - vesical manifestations of allergy, 589–590
  - congenital
    - bladder ears, 587
    - diverticulum, 587
    - exstrophy, 585–586
    - megacystis, 587
    - persistent urachus, 586, 586*f*
- Bladder diverticula, 493, 493*f*
- Bladder ears, 587
- Bladder injuries, 299–300
  - clinical findings, 300
    - laboratory findings, 300
    - signs, 300
    - symptoms, 300
    - x-ray findings, 300–301, 301*f*
  - complications, 301
  - extraperitoneal bladder rupture, 301
  - intraperitoneal rupture, 301
  - pathogenesis and pathology, 300, 300*f*
  - pelvic fracture, 301
  - pelvic hematoma, 301–302
  - prognosis, 302
  - treatment, 301–302
- Bladder neck suspension, 503
- Bladder outlet obstruction
  - clinical manifestation of, 492
  - symptoms of, 36–37
  - urodynamic evaluations of, 496
- Bladder outlet obstruction index, 492
- Bladder pain syndrome. *See* Interstitial cystitis
- Bladder substitution. *See* Urinary diversion
- Bladder tumor antigen test (BTA), 55
- Bleomycin, 409*t*
- Blinatuimomab, 418
- α-blockers, for BPH, 597, 597*t*
- Blood urea nitrogen, 58
- Bloody urine, 37–38
- Bosniak classification, for renal masses, 330–331, 331*t*
- Botulinum toxin-sensitive mechanisms, in micturition, 464–465
- Botulinum-A toxin, 505

Bowman's capsule, 17
Brachytherapy, 422–423, 423*f*
Bromocriptine, 616
Brush biopsy, ureteral catheterization for, 120, 120*f*
BTA stat test, 313
BTA TRAK assay, 313
Bulking material, 503–504
"Bystander effect," 417

C

Cabazitaxel, 409*t*
Cabergoline, 515
Calcium
  reabsorption defects of, 548
  supplementation of, for calculi prevention, 284
Calcium channels, in micturition, 462
Calcium nephrolithiasis, 262
Calculi, 259–287
  bladder, 125, 285, 286*f*, 287*f*
  prostatic, 285–286, 599*f*–600*f*, 599–600
  renal and ureteral (*See* Renal and ureteral stones)
  seminal vesicle, 285–286
  urethral and preputial, 287
  in urinary diversion/bladder substitution, 403
Calymmatobacterium granulomatis, 251
Candida albicans, 234
Candidiasis, 234–235
  risk factors for, 234, 234*t*
  treatment of, 235
CAPRA score, 362, 362*f*
Carboplatin, 409*t*
Carcinoma in situ (CIS), testicular, 379, 412
Cardiovascular disease (CAD), and testosterone levels, 742
CAR-T cell therapy, 418
Carter-Thomason device, 156*f*
Case–control study, 783–784
Castration-resistant prostate cancer (CRPC), 413
Catheter-directed thrombolysis, 115
Cauda equina syndrome, 477
Caverject, 620
Cavernosography, 614, 614*f*
Cavernosometry, 614
Cavernous arterial occlusion pressure, 614
Cavernous artery systolic occlusion pressure (CASOP), 614
Cavernous veno-occlusive dysfunction (CVOD), 610
Cellules, 178, 178*f*
Cellulose phosphate, 284
Cephalosporins, for urinary tract infection, 208
Cerebellar ataxia, 717
Cerebrovascular accident, 474
Cervix
  description of, 632
  infection of, 44
Chancroid
  diagnosis of, 250–251
  etiology and clinical presentation of, 250
  treatment of, 249*t*, 251
Charlson Comorbidity Index, 565, 566*t*
Checkpoint inhibitors, 416–417, 419
Chemical shift imaging, 91
Chemotherapy
  bladder cancer treated with, 319–320
  germ cell tumors treated with, 408, 410–411
  metastatic bladder cancer treated with, 412
  metastatic renal cell carcinoma treated with, 412
  transitional cell carcinoma treated with, 411–412
  Wilms tumor treated with, 345
Chimeric antigen receptors, 418
Chlamydia trachomatis, 38
  urethritis by, 244
Choline, 360
Choriocarcinoma, 379
Chronic hemodialysis, 560–561
Chronic kidney disease (CKD), 557–562
  etiology, 337, 557–558
  historical background, 557
  history examination, 559
  laboratory findings
    blood testing, 559–560
    renal biopsy, 560
    urine composition, 559
    x-ray findings, 560
  symptoms and signs, 558–559
  treatment, 560–562
    chronic hemodialysis, 560–561
    chronic peritoneal dialysis, 560
    renal transplantation, 561–562
Chronic peritoneal dialysis, 560
Chronic urinary retention, 37
Chyluria, 37, 240
Circumcaval ureter. *See* Retrocaval ureter
Circumcision, 653
Cis-gender, 747
Cisplatin, 409*t*
Clean intermittent catheterization (CIC), 480, 506
Clear cell renal adenocarcinoma, 330*f*
Clinical significance, 788, 789*t*
Clinical trial
  case–control study versus, 783–784
  cohort study versus, 784
  comparison group in, 784–785
  definition of, 781, 784
  ecological studies versus, 782–783
  effectiveness of, 786
  efficacy of, 786
  epidemiologic study designs versus, 781–782
  intention to treat, 786
  masking in, 785
  phases of, 785–786
  randomized controlled trial, 785
Clitoral bulbs, 633
Clitoris, 632–633
Clitoroplasty, 697*f*, 697–698, 698*f*
Cloacal exstrophy, 696, 696*f*
Clomiphene citrate, for male infertility, 729–730
Cloudy urine, 37
Cohort study, 784
Colon conduit, 392, 394*f*
Color Doppler, 77
Color duplex ultrasound, for erectile dysfunction, 613, 613*f*
Combination therapy
  for benign prostatic hypertrophy, 597–598
  for bladder cancer, 320–321
Communicating hydrocele, 773
Complete androgen insensitivity syndrome, 681*t*, 687–688
Compliance, 490–491
Computed tomography (CT), 81–86, 87*f*–92*f*

  advantages and disadvantages, 85–86
  angiomyolipoma on, 341
  clinical applications, 81, 84–85
  comparison with other methods, 100*f*–103*f*
  dual-energy, 85
  helical, 91*f*
  principles, 81
  renal, 81
  renal cell carcinoma on, 331, 332*f*
  renal pelvic tumor, 322
  spiral, 81
  Wilms tumor on, 344
Condylomata acuminata, urethral, 655–656
Confounding, 782
Congenital adrenal hyperplasia (CAH)
  description of, 685–687, 687*f*
  male infertility and, 729
Congenital bilateral adrenal androgenic hyperplasia
  laboratory findings, 516
  pathophysiology, 515–516
  prognosis, 516
  symptoms and signs, 516
  treatment, 516
  x-rays and CT scans, 516
Congenital cystinuria, 548
Contrast media, in uroradiography, 63–64
Corticosteroids, for nephrotic syndrome, 545
Costovertebral angle (CVA), 41
Cough leak point pressure (CLPP), 494
Creatinine clearance, 57–58
Cremasteric muscle reflex, 774
Cryosurgery, for prostate cancer, 368–369
Cryotherapy, for small renal masses, 140–141
Cryptorchidism, 26, 722
Cushing's syndrome, 510–515
  clinical findings
    imaging studies, 512*f*, 513–514
    laboratory findings, 512–513
    symptoms and signs, 512
  pathology, 511, 511*f*
  pathophysiology, 511
  prognosis, 515
  treatment, 514–515
Cyclic adenosine monophosphate (cAMP), 609
Cyclophosphamide, 309
Cyst(s)
  in prostate gland, 599–600
  renal (*See* Renal cysts)
Cystic fibrosis, 723
Cystine calculi, 285
Cystitis, 37, 222
  acute, 216
  interstitial (*See* Interstitial cystitis)
  recurrent, 216–217
Cystography/cystourethrography, 71, 71*f*–75*f*
Cystometry. *See also* Urodynamics
  bladder contractions during, 490
  bladder sensations during, 489–490
  capacity, 491–492
  compliance, 490–491
  definition of, 488
  detrusor overactivity, 490
  technique for, 488–489
  urethral catheters used in, 488
Cystoscopy, 119–120
  for BPH, 596
Cytokines, 416
Cytomegalovirus (CMV), 564
Cytoreductive nephrectomy, for metastatic renal cell carcinoma, 339
Cytotoxic T-lymphocyte-associated protein 4 (CTLA–4), 415–416
Cytoxan. *See* Cyclophosphamide

D

Da Vinci surgical system, 151, 152*f*, 167–169, 168*f*–169*f*. *See also* Robotic surgery
Dapoxetine hydrochloride, 622
De Toni-Fanconi-Debré syndrome, 548
Defective DNA mismatch repair, 720
Dehydroepiandrosterone (DHEA), 744–745
Dendritic cells, 415
Denonvillier's fascia, 753, 755*f*
Desmopressin, 479
Detrusor external sphincter dyssynergia (DESD), 488, 493–495
Detrusor leak point pressure (DLPP), 494
Detrusor overactivity, 490
Dexamethasone, 512
Diabetes mellitus
  erectile dysfunction associated with, 611
  urinary tract infection in, 223
Diffusion-weighted imaging, 95
5α-Dihydrotestosterone (DHT), 672, 744
Dimercaptosuccinic acid (DMSA), 184, 187
Disability, 635
Dismembered pyeloureteroplasty, 577
Disorders of sex development (DSD), 671
  atypical genitalia, 671, 676–677
    algorithm for initial workup of, 685*f*
    biochemical evaluation, 679, 683*f*
    chromosomal evaluation, 679
    diagnostic laparotomy/laparoscopy, 679, 683
    differential diagnosis, 686*t*
    history examination, 677
    physical examination, 677, 682*f*
    radiographic evaluation, 679, 684*f*
    sex assignment, 683, 685
  cloacal exstrophy, 696, 696*f*
  female pseudohermaphrodites, 685–687
    congenital adrenal hyperplasia and, 685–687, 687*f*
    maternal medications and, 687, 687*t*
    maternal tumors and, 687
  gonadal function syndromes, abnormal
    17β-hydroxysteroid dehydrogenase deficiency, 692
    mixed gonadal dysgenesis, 691–692, 692*f*
    Swyer's syndrome, 691
    Turner's syndrome, 691
    46,XX complete gonadal dysgenesis, 691
  hypospadias, 693–695, 694*f*
  male pseudohermaphrodites, 687–689
    complete androgen insensitivity in, 687–688
    differential diagnosis, 688*f*
    partial androgen insensitivity in, 688*f*, 688–689
  micropenis, 695*f*, 695*t*, 695–696, 776
  ovotesticular, 692–693, 693*f*
  persistent Müllerian duct syndrome, 690*f*, 690–691
  5α-reductase type 2 deficiency, 689*f*–690*f*, 689–690

Disorders of sex development (DSD) (*Cont.*):
  sexual differentiation
    disorders of, 676, 678*t,* 679*t,* 680*t*–681*t*
    normal, 671–676, 672*f*–677*f*
  surgical management
    clitoroplasty, 697–698
    female external genitalia reconstruction, 699*f*
    phallic reconstruction, 701
    urogenital sinus repair, 700*f*
    vaginoplasty, 698–699, 699*f,* 700*f,* 701
Diuretics, for calculi prevention, 284
Diverticulum, 587
Docetaxel, 318, 409*t*
Dopamine mechanisms, in micturition, 458
Dosage-sensitive sex reversal (DAX-1), 671
Double-J catheters, 122
Doxazosin, for BPH, 597
Doxorubicin, 409*t*
Dual-energy x-ray absorptiometry (DEXA), 741
Ductus deferens, MRI, 98*f*
Duloxetine
  for detrusor overactivity, 457
  for urinary incontinence, 503
Duplication, ureteral
  clinical presentation, 571–572
  complete, 571, 572*f*
  description of, 20
  imaging, 572
  incomplete, 571, 572*f*
  treatment, 572
Dysfunctional voiding, 494
Dyspareunia, 637*t,* 640
Dysuria, 36

E

Ebola virus, 254–255
Echinococcosis, 240–241
  clinical findings, 240*f,* 240–241
  etiology of, 240
  prognosis of, 241
  treatment of, 241
Echinococcus granulosus, 240
Ecological studies, 782–783
Ectopic ACTH syndrome, 514
Ectopic kidney, 20, 530
  crossed ectopy without fusion, 530
  simple, 530
Ectopic testis, 26
Ectopic ureters, 575, 575*f*
Eculizumab, 566
Edema, 38
Edex, 620
Effectiveness, 786
Efficacy, 786
Ejaculation, 622
Ejaculatory ducts, 12
  MRI, 98*f*
Elderly, laboratory values in, 59*t*
Electrohydraulic probes, 144
Electromyography (EMG), 488
Embryonal cell carcinoma, 378
Emission, 622
Emphysematous pyelonephritis, 210–211
Endorectal magnetic resonance imaging, for prostate cancer, 359
Endoscopic intrarenal instrumentation, 135–136
End-stage renal disease (ESRD), 557, 558*f*–559*f,* 563–564. *See also* Chronic kidney disease (CKD)
Enuresis, 36
Epidemiologic studies
  clinical trial versus, 781–782
  designs of, 781–782, 782*f*
Epididymal sperm aspiration, 727, 727*f*
Epididymis, 773
  anatomy, 9*f,* 13
  blood supply, 13
  histology, 13
  lymphatics, 13
  physical examination, 43
  relations, 13
  tumors, 385–386
Epididymitis
  classification, 247
  definition, 247
  description of, 220–221
  diagnosis, 247
  etiology, 247
  in HIV patients, 222–223
  treatment, 247*t,* 247–248
Epididymoorchitis, 247, 773–774
Epididymovasostomy, 725–726
Epispadias, 24, 28, 44, 650*f,* 651, 775
Epithelial cell casts, 53
Epithelial cells, 53
Erectile dysfunction (ED), 605, 609. *See also* Penile erection
  advanced testing for, 612–615, 613*t*
  aging and, 611
  anorgasmia, 609
  arterial disorders and, 610
  cavernosal disorders and, 610–611
  classification and pathogenesis, 610*t*
  diabetes mellitus and, 611
  diagnosis and treatment, 612
    follow-up strategy, 621
    medical/sexual/psychosocial history, 612
    physical/laboratory examination, 612
    questionnaires/laboratory investigations, 612
  epidemiology, 609
  hormonal disorders and, 610
  medication-induced, 611
  neurogenic disorders and, 610
  neurologic tests, 615
    biothesiometry, 615
    penile thermal sensory testing, 615
  nocturnal penile tumescence test, 615
  nonsurgical treatment, 615
    hormonal therapy, 616–617
    lifestyle changes, 615–616
    medication changes, 616
    psychosexual therapy, 616
  penile prostheses, 621*t,* 621–622
  penile vascular function tests, 612–614
    arteriography, 614
    cavernosometry and cavernosography, 614, 614*f*
    cavernous arterial occlusion pressure, 614
    color duplex ultrasonography, 613, 613*f*
    combined intracavernous injection and stimulation test, 612–613
  penile vascular surgery, 621

  - pharmacologic therapy
    - centrally acting oral agents, 619
    - intracavernous injection, 619–620, 620*t*
    - phosphodiesterase inhibitors, 617–619
    - transurethral therapy, 619
    - vacuum constriction device, 620–621
  - premature ejaculation, 609
  - psychological disorders and, 609–610
  - psychological evaluation, 615
  - pulmonary disease and, 611
  - retarded ejaculation, 609
  - retrograde ejaculation, 609
- Erection. *See* Penile erection
- Erythrocyte casts, 53, 539–540, 542
- *Escherichia coli,* 714
- Estradiol, 703
- Ethics, 788–789
- Etoposide, 409*t*
- European Randomized Study of Screening for Prostate Cancer (ERSPC), 364
- Excretory urography (EU). *See* Intravenous urography (IVU)
- ExoDX Prostate Intelliscore, 56, 357
- Expected posttransplant survival score, 563
- Exposure, 781
- Exstrophy, bladder, 28, 585–586
- External genitalia, in females
  - adults, 633
  - children, 776–778
- External-beam radiotherapy (EBRT), 421, 433. *See also* Radiotherapy
- Extragonadal germ cell tumors, 385
- Extravesical ureteroneocystostomy, 567

F

- Female genital arousal disorder (FGAD), 637*t,* 638–639
- Female genitalia
  - internal, 673
  - physical examination, 44
- Female orgasm disorder, 637*t,* 639
- Female sexual dysfunction
  - classification of, 636–640, 637*t*
  - description of, 635–636
  - female genital arousal disorder, 637*t,* 638–639
  - female orgasm disorder, 637*t,* 639
  - hypoactive sexual desire disorder, 636–638, 637*t*
  - persistent genital arousal disorder, 637*t,* 639
  - sexual pain disorders, 637*t,* 640
- Female sexual response, 631–632, 632*f,* 632*t*
- Female urethra disorders
  - acquired diseases
    - acute urethritis, 661
    - atrophic urethritis, 661–662
    - chronic urethritis, 661
    - prolapse of urethra, 663
    - urethral caruncle, 662–663
    - urethral diverticulum, 664–668
    - urethral stricture, 668
    - urethrovaginal fistulas, 663–664
  - congenital anomalies
    - distal urethral stenosis, 659–660, 660*f*
    - labial fusion, 660
- Feminizing (male to female) gender-affirming surgery, 750–759
  - bilateral orchiectomy in, 751, 751*t*
  - complications of, 758–759
  - criteria for, 750, 750*t*
  - definition of, 748
  - description of, 749–750
  - types of, 749*t*
  - vaginal canal, 756–758
  - vaginoplasty, 751–756, 753*t*–754*t,* 755*f*–758*f*
- Fertilization, 707
- Fibroblast growth factor receptor 3 (FGFr3), 309–310
- Fibromuscular dysplasia, 113
- Filariasis
  - cystoscopy of, 240
  - etiology of, 239
  - laboratory findings, 239–240
  - pathogenesis, 239
  - pathology, 239
  - prevention, 240
  - prognosis, 240
  - retrograde urography, 240
  - signs of, 239
  - symptoms of, 239
  - treatment, 240
- Finasteride, 597
- Fine-needle aspiration (FNA), of testis, 716, 716*f*
- Finite amplitude emitters, 279
- 5-item version (IIEF-5), for erectile dysfunction, 612
- Flibanserin, 638
- Fluciclovine, 360
- Fluoroquinolones, for urinary tract infection, 207
- Fluoroscopy-guided renal access, 131–132
- Focal glomerulosclerosis, 544
- Focal therapy, for prostate cancer, 369
- Follicle-stimulating hormone (FSH), 703, 704
- Folliculin, 341
- Foreign body in bladder, 589
- Foreskin, 774–775, 775*f*
- Functional profile length, 488

G

- GABA mechanisms, in micturition, 457–458
- Gabapentin, for detrusor overactivity, 457–458
- Gadolinium, 90
- Gamma-glutamyl transpeptidase (GGT), 381
- Gastrointestinal tract
  - autonomic nerve supply to, 33*f*
  - sensory nerves of, 34*f*
- Gemcitabine, 317–318, 409*t*
- Gemzar. *See* Gemcitabine
- Gender, 747
- Gender dysphoria
  - definition of, 747–748
  - medical exam-induced, 748
  - treatment of, 749
- Gender identity, 747
- Gender identity disorder, 748
- Gender nonconforming/gender non-binary, 747
- Gender nonconformity, 747
- Gender-based violence, 635
- Genital duct system
  - anomalies, 27
    - azoospermia, 27
    - congenital absence, 27
    - duplication, 27

- Genital duct system (*Cont.*):
  - development, 26
  - female, 27
  - male
    - ejaculatory duct, 26–27
    - epididymis, 26
    - prostate, 27
    - seminal vesicles, 26–27
    - vas deferens, 26–27
- Genital tract infections, male, 714, 714*t*
- Genital tuberculosis, 234. *See also* Tuberculosis
- Genital tumors, 377–389
  - epididymis tumors, 385–386
  - extragonadal germ cell tumors, 385
  - germ cell tumors of testis, 377–384
  - non–germ cell tumors of testis, 384–385
    - gonadoblastomas, 384–385
    - Leydig cell tumors, 384
    - Sertoli cell tumors, 384
  - penile tumors, 386–389
  - scrotal lesion, 389
  - secondary tumors of testis, 385
    - leukemia, 385
    - lymphoma, 385
    - metastatic tumors, 385
  - spermatic cord tumors, 386
- Genital ulcer, 248–253, 249*t*
  - chancroid
    - diagnosis of, 250–251
    - etiology and clinical presentation of, 250
    - treatment of, 249*t*, 251
  - diagnosis of, 248
  - etiology of, 248
  - granuloma inguinale
    - clinical presentation of, 251
    - etiology and epidemiology of, 251
    - treatment of, 249*t*, 251
  - herpes simplex virus (HSV) infection
    - clinical presentation of, 248
    - epidemiology of, 248
    - etiology of, 248
    - treatment of, 248–249, 249*t*
  - lymphogranuloma venereum
    - clinical presentation, 251
    - etiology, 251
    - treatment, 249*t*, 251
  - syphilis
    - clinical presentation of, 249–250
    - diagnosis of, 250
    - treatment of, 249*t*, 250
  - warts, 251–253, 252*t*
    - diagnosis of, 252
    - etiology of, 251–252
    - treatment of, 252*t*, 252–253
- Genitalia, external
  - anomalies, 28
  - female, 28
  - male, 27–28
- Genitourinary tract
  - anatomy of, 1–16
    - adrenal gland, 1, 3*f*
    - bladder, 7*f*, 7–8, 9*f*–11*f*
    - calices, 5*f*, 7
    - epididymis, 9*f*, 13
    - female urethra, 15
    - kidneys, 1–7, 3*f*–6*f*
    - penis and male urethra, 10*f*, 14–15
    - prostate gland, 7*f*, 8–12, 9*f*–12*f*
    - renal pelvis, 5*f*, 7, 7*f*
    - scrotum, 14
    - seminal vesicles, 7*f*, 9*f*, 12–13
    - spermatic cords, 9*f*, 13
    - testis, 9*f*, 13–14
    - ureter, 3*f*, 5*f*, 7, 7*f*
  - autonomic nerve supply to, 33*f*
  - bacterial infections of (*See* Urinary tract infection [UTI])
  - embryology, 17–28
    - genital duct system, 22*f*, 25*f*, 26
    - genitalia, external, 27–28
    - gonads, 24–26, 25*f*
    - nephric system, 17–20, 18*f*
    - vesicourethral unit, 20–23, 21*f*–23*f*
  - infections of, 229–241
    - actinomycosis, 235
    - candidiasis, 234*t*, 234–235
    - echinococcosis, 240–241
    - filariasis, 239–240
    - schistosomiasis, 235–239, 237*f*–238*f*
    - tuberculosis, 229–234, 230*f*, 233*f*
  - injuries to (*See* Injuries, genitourinary tract)
  - male, 2*f*
  - physical examination (*See* Physical examination, of genitourinary tract)
  - sensory nerves of, 34*f*
  - symptoms of disorders of, 31–39
    - anuria, 37
    - bladder outlet obstruction, 36–37
    - bloody ejaculation, 38
    - bloody urine, 37–38
    - chyluria, 37
    - cloudy urine, 37
    - dysuria, 36
    - edema, 38
    - enuresis, 36
    - epididymal pain, 35
    - fever, 31
    - frequency of urination, 36
    - gastrointestinal, 35
    - gynecomastia, 38
    - incontinence, 37
    - local and referred pain, 31
    - and mimicry, 35
    - nocturia, 36
    - oliguria, 37
    - pneumaturia, 37
    - prostatic pain, 35
    - related to act of urination, 36
    - renal pain, 31–32, 32*f*
    - sexual problems, 38–39
    - skin lesions of external genitalia, 38
    - systemic manifestations, 31
    - testicular pain, 35
    - ureteral pain, 32, 32*f*
    - urethral discharge, 38
    - urgency, 36–37
    - vesical pain, 32, 35
    - visible/palpable mass, 38
    - weight loss, 31

Germ cell tumors, 377–384
  advanced, chemotherapy for, 410–411
  classification, 377
  clinical findings
    imaging, 381
    laboratory findings, 380–381
    signs, 380
    symptoms, 379–380
    tumor markers, 380*t,* 380–381
  clinical staging, 379, 380*t*
  differential diagnosis, 381
  epidemiology, 377
  follow-up care, 383
  metastatic patterns of, 379
  overview of, 410
  pathology
    carcinoma in situ, 379, 412
    choriocarcinoma, 379
    embryonal cell carcinoma, 378
    mixed cell types, 379
    seminoma, 378
    teratomas, 379
  prognosis, 383–384
  risk factors, 377
  treatment, 381
    adjunctive surgery, 411
    chemotherapy, 408, 410–411
    high-stage NSGCTs, 382–383, 383*f,* 383*t*
    high-stage seminoma, 382
    low-stage NSGCTs, 382
    low-stage seminoma, 381–382
    "salvage," 411
  tumorigenic model for, 377–378, 378*f*
Germ cells, 705–706, 706*f*
Glans clitoris, 633
Glans penis, 756*f*
Gleason score, 358
Glial cell–derived neurotrophic factor (GDNF), 18–19
Glomerular basement membrane, antigens with, 541
Glomerular filtration rate (GFR), 57, 557
Glomerulonephritis, 541–543
  antibodies deposition in glomerulus, 541
  clinical manifestations, 541
  IgA nephropathy, 543
  immunologic mechanisms, 541
  poststreptococcal, 542–543
  rapidly progressive, 543
Gonad(s)
  anomalies, 26
  descent of
    ovaries, 26
    testis, 24, 26
  development, 24
  differentiation of, 671–672, 672*f*
Gonadal agenesis, 26
Gonadoblastomas, 384–385, 691
Gonadotropin-releasing hormone (GnRH), 703–704, 704*t*
Gonococcal infection, 245
Gonococci, 44
Goodpasture's disease, 543
Graft intolerance syndrome, 111
Granular casts, 53, 540
Granuloma inguinale
  clinical presentation of, 251
  etiology and epidemiology of, 251
  treatment of, 249*t,* 251
Granulomatous prostatitis, 219
Groin flaps, 761*f,* 762–763, 766
"G-spot," 633
Guanite, 259
Gynecomastia, 38
  testosterone therapy and, 743

H

Haemophilus ducreyi, 248, 250
Hand-assisted laparoscopic surgery (HALS), 151, 151*f*
Hassan cannula technique, 152–154, 153*f*
Hasson-type ports, 154, 154*f*
Hemangiomas, 342
Hematuria, with renal colic, 38
Hemorrhage
  pelvic, transcatheter embolization for, 109–110
  urinary tract, embolization for, 107
Hemorrhagic cystitis, 592
  after radiation therapy, 592, 593*f*
Hereditary leiomyomatosis, 335
Hereditary nephritis, 547
Hereditary papillary renal carcinoma, 335
Herpes simplex virus (HSV) infection
  clinical presentation of, 248
  epidemiology of, 248
  etiology of, 248
  treatment of, 248–249, 249*t*
High-dose-rate brachytherapy, 368
Hinman's syndrome, 660
HIV/AIDS, 253–254
  acute retroviral syndrome, 253–254
  and circumcision, 254
  diagnostic testing for, 253
  initial management of, 254
  urinary tract infection in, 222–223
Holmium laser enucleation of prostate (HoLEP)
  for benign prostatic hyperplasia, 598
  for prostatic adenoma enucleation, 124
Home dialysis, 561
Hormonal disorders, in infertility, 712–713, 713*t*
Hormonal therapy, for erectile dysfunction, 616–617
Horseshoe kidney, 20, 528, 529*f*
24-hour urinary cortisol level, for Cushing's syndrome, 513
Human chorionic gonadotropin (hCG), 380–381, 744
Hydatid disease. *See* Echinococcosis
Hydrocele, 772–773
Hydrochlorothiazides, 263
Hydrogen ion secretion defects, 549
Hydrometrocolpos, 777
Hydronephrosis, 41, 179
  bilateral, 181*f*
  unilateral, 182–184, 183*f*
Hydroureteronephrosis, vesicoureteral reflux and, 195
21α-Hydroxylase deficiency, 516, 685–687
17β-Hydroxysteroid dehydrogenase deficiency, 681*t,* 692
Hymeneal tag, 777*f*
Hypercalcemia
  parathyroid hormone-related peptide as cause of, 329
  renal cell carcinoma and, 329

- Hyperoxaluric calcium nephrolithiasis, 264
- Hyperprolactinemia
  - description of, 729
  - infertility and, 717–718
- Hypertension, 114
- Hyperuricosuric calcium nephrolithiasis, 264
- Hypoactive sexual desire disorder (HSDD), 636–638, 637*t*
- Hypocitraturic calcium nephrolithiasis, 265
- Hypofractionation, 426
- Hypogenesis, 26
- Hypoosmotic swelling test, 712
- Hypoplasia, 521–522
- Hypospadias
  - classification, 649
  - description of, 24, 28, 649, 650*f*, 693–695, 694*f*
  - differential diagnosis, 651
  - laboratory findings, 649, 651
  - midshaft, 775*f*
  - proximal, 776*f*
  - symptoms and signs, 649
  - treatment, 651
- Hypothalamic–pituitary–gonadal (HPG) axis
  - anatomy of, 703–704, 704*f*
  - anterior pituitary gland, 704–705
  - feedback loops, 703
  - hormone classes, 703, 704*f*
  - hypothalamus, 703–704
  - role of, 703
  - testis, 705
- Hypothalamus, 703–704, 704*f*
- Hypothyroidism, and male infertility, 729
- Hypoxia-inducible factor-alpha, 339

I

- Idiopathic epididymal obstruction, 723
- Ifosfamide, 409*t*
- Ileal conduit urinary diversion, 392, 393*f*
- Image-guided radiotherapy, 426
- Imaging. *See* Radiology; *specific technique*
- Immotile cilia syndromes, 723–724
- Immune-related adverse events (IRAEs), 417
- ImmunoCyt, 313
- Immunoediting, 415–416
- Immunoglobulin A nephropathy, 543
- Immunology, 415–416
- Immunotherapy
  - antibodies, 417
  - Bacillus Calmette–Guerin, 416
  - bladder cancer treated with, 320
  - checkpoint inhibitors, 416–417, 419
  - chimeric antigen receptors, 418
  - cytokines in, 416
  - goal of, 415
  - immunoediting, 415–416
  - interferon alfa, 416
  - interleukin 2, 416
  - metastatic renal cell carcinoma treated with, 340–341
  - principles of, 415–416
  - prostate cancer treated with, 418–419
  - renal cell carcinoma treated with, 419–420
  - T-cell engagement as, 418
  - vaccines, 417–418
- In vitro fertilization, 730–731
- Incidentaloma
  - diagnostic algorithm, 510
  - differential diagnosis, 510*t*
  - imaging, 509–510, 518*f*
  - metabolic evaluation, 509
- Incontinence
  - description of, 37
  - urinary (*See* Urinary incontinence)
- Indwelling catheters, for neurogenic bladder, 480
- Infections. *See also specific infection*
  - genitourinary tract, 229–241
  - urinary tract (*See* Urinary tract infection [UTI])
- Infertile male syndrome, 681*t*
- Infertility, male, 703–731
  - adjunctive tests
    - semen culture, 714
    - urinalysis, 714
  - assisted reproductive technologies, 730–731
    - in vitro fertilization and ICSI, 730*f,* 730–731
    - intrauterine insemination, 730
    - preimplantation genetic diagnosis, 731
  - diagnosis, 707–716
  - fine-needle aspiration of testis, 716, 716*f*
  - genetic tests
    - chromosomal studies, 713
    - cystic fibrosis mutation testing, 713
    - Y chromosome microdeletion analysis, 713
  - history evaluation, 708*t,* 708–709, 709*t*
  - laboratory testing, 710–713
    - adjunctive semen tests, 712
    - antisperm antibody test, 712
    - hormone assessment, 712–713, 713*t*
    - hypoosmotic swelling test, 712
    - semen analysis, 710–712, 711*t*
    - sperm DNA fragmentation assay, 712
    - sperm penetration assay, 712
  - male reproductive physiology and, 703–707
  - nonreproductive implications of, 731
  - nonsurgical treatments
    - antioxidant therapy, 730
    - clomiphene citrate, 729–730
    - coital therapy, 728–729
    - hormone therapy, 729
    - immunologic infertility, 729
    - leukocytospermia, 728
  - physical examination, 709
  - posttesticular causes, 722*t*
    - adult polycystic kidney disease, 723
    - bacterial infections, 723
    - coital timing and frequency, 724
    - cystic fibrosis, 723
    - ejaculatory ducts blockage, 723
    - functional blockages, 723
    - groin and hernia surgery, 723
    - hypospadias, 724
    - idiopathic epididymal obstruction, 723
    - immotile cilia syndromes, 723–724
    - immunologic infertility, 724
    - infections, 723
    - vasectomy, 723
    - Young syndrome, 723
  - pretesticular causes
    - androgens excess, 718
    - congenital hypogonadotrophic syndromes, 717
    - estrogens excess, 718

- gonadotropin deficiency, 717
    - hyperprolactinemia, 717–718
    - hyperthyroidism, 718
    - hypothyroidism, 718
    - isolated gonadotropin deficiencies, 717
    - pituitary insufficiency, 717
  - radiologic testing
    - computed tomography, 714–715
    - magnetic resonance imaging, 714–715
    - scrotal ultrasound, 714, 714*f*
    - transrectal ultrasound, 714, 715*f*
  - surgical treatments, 724–728
    - ejaculatory duct obstruction, 726, 726*f*, 726*t*
    - electroejaculation, 726–727
    - orchidopexy, 728
    - pituitary ablation, 728
    - sperm retrieval, 727*t*, 727–728
    - varicoceles, 724–725, 725*t*
    - vasectomy reversal, 725*f*, 725–726
  - testicular causes, 718*t*, 718–722
    - androgen receptor deficiency, 721
    - cryptorchidism, 722
    - defective DNA mismatch repair, 720
    - diabetes mellitus, 721
    - drugs, 720, 720*t*
    - idiopathic, 722
    - Klinefelter syndrome, 719
    - liver cirrhosis, 721
    - myotonic dystrophy, 719
    - Noonan syndrome, 719
    - orchitis, 721
    - radiation, 720
    - 5α-reductase deficiency, 721
    - renal failure, 720–721
    - Sertoli-cell-only syndrome, 719–720
    - sickle cell disease, 721
    - torsion, 721
    - trauma, 721–722
    - vanishing testis syndrome, 719
    - varicocele, 722
    - XX male syndrome, 719
    - XYY syndrome, 719
    - Y chromosome microdeletions, 718
  - testis biopsy and vasography, 715–716
- Inguinal canal, 773
- Inguinal hernia, 772*f*, 772–773
- Inhibin, 705
- Injuries, genitourinary tract
  - bladder, 299–302
  - emergency diagnosis and management
    - algorithms for staging urogenital trauma, 292*f*–293*f*
    - catheterization, 291
    - history and physical examination, 291
  - kidney, 291–298
  - penis, 306
  - scrotum, 306
  - testis, 306
  - ureter, 298–299
  - urethra
    - anterior, 304–306
    - posterior, 302*f*, 302–304
- Innate immunity, 415
- Intensity-modulated radiotherapy (IMRT), 425–426
- Intention to treat, 786
- Interferon alfa, 416
- Interferon-alpha, 318
- Interleukin 2, 416
- International Continence Society (ICS), 499
- International Prostate Symptom Score (IPSS), 594, 595*t*
- International Society of Impotence Research, 609
- Intersex disorders. *See* Disorders of sex development (DSD)
- Interstitial cystitis
  - diagnosis, 588–589
  - differential diagnosis, 589
  - etiology, 588
  - prognosis, 589
  - sign and symptoms, 587
  - treatment, 589
- Interstitial nephritis, 546
- Intestinal vaginoplasty, 757–758
- Intracavernous injection (ICI) of vasoactive agents, 605, 619, 620*t*
  - adverse effects, 620
  - alprostadil, 620, 620*t*
  - contraindications, 620
  - dosage and administration, 620
  - drug combinations, 620, 620*t*
  - papaverine, 619, 620*t*
  - priapism treated with, 619–620
- Intrauterine insemination (IUI), 730
- Intravenous pyelography (IVP). *See* Intravenous urography (IVU)
- Intravenous urography (IVU), 64–65, 67*f*, 68
  - patient preparation in, 64–65
  - technique in, 65
  - technique modifications in, 65
- Intrinsic sphincter deficiency, 487
- Ion channels, in micturition, 462
- Ipilimumab, 416, 419–420
- Ischemic priapism, 625
- 15-item International Index of Erectile Function (IIEF), 612

J

- Jejunal conduit urinary diversion, 392
- Juxtaglomerular cell tumor, 342

K

- Kallmann syndrome, 717, 729
- Kaposi sarcoma, of penis, 388
- Ketoconazole, for Cushing's syndrome, 515
- Kidney(s). *See also specific renal entries*
  - anatomy, 1–3, 3*f*–5*f*
  - blood supply, 3*f*, 4, 5*f*–6*f*
  - cessation of function, with transcatheter embolization, 111–112
  - computed tomography of, 88*f*–91*f*
  - ectopic, 20
  - fluoroscopy-guided access to, 131–132
  - histology, 3–4
    - nephron, 3–4, 5*f*
    - supporting tissue, 4
  - horseshoe, 20
  - lymphatics, 7
  - magnetic resonance imaging of, 93*f*
  - malrotated, 20
  - metastases of, 346
  - nerve supply, 4
  - percutaneous access to, 129–130, 130*t*
  - physical examination, 41–42, 42*f*
  - relations of, to other organs, 3, 3*f*–4*f*

Kidney(s) (*Cont.*):
  solitary, 20
  supernumerary, 20
  ultrasonography of
    description of, 77, 79, 82*f*
    renal access guided with, 130–131, 131*f*
Kidney disorders, 521–534
  acquired
    arteriovenous aneurysm, 533–534, 534*f*
    arteriovenous fistula, 533
    renal artery aneurysm, 531–532
    renal infarcts, 532–533
    renoalimentary fistula, 534, 534*f*
    renobronchial fistula, 534
    thrombosis of renal vein, 533, 533*f*
  analgesic nephropathy, 546
  collagen diseases, 546
  congenital, 521
    abnormal rotation, 530
    abnormalities of vessels, 531
    agenesis, 521
    dysplasia, 522
    ectopic kidney, 530
    hypoplasia, 521–522
    medullary sponge kidney, 530
    multicystic kidney, 522
    polycystic kidney disease, 522*f,* 522–525, 524*f*
    renal fusion, 528–530, 529*f*
    simple cyst, 525*f,* 525–527
    supernumerary kidneys, 522
  distal tubule anomalies, 549
  glomerulonephritis (*See* Glomerulonephritis)
  hereditary, 547
    chronic hereditary nephritis, 547
    cystic disease of renal medulla, 548
    polycystic kidneys, 547–548
  history and physical examination, 539
  imaging, 540
  interstitial nephritis, 546
  laboratory findings, 539–540
  medical diseases, 539–549
  myelomatosis, 547
  nephrotic syndrome, 543–546
  obstructive uropathy, 546–547
  proximal tubule anomalies, 548–549
  renal biopsy, 540–541
  renal diabetes insipidus, 549
  uric acid nephropathy, 546
Kidney Donor Profile Index (KDPI), 563
Kidney injuries, 291
  classification of, 291, 295
  clinical findings, 295–297
  complications, 297
  differential diagnosis, 297
  early pathologic findings, 291, 294*f,* 295
  etiology, 291, 294*f*
  laboratory findings, 296
  late pathologic findings, 295*f*
    arteriovenous fistulas, 295
    hydronephrosis, 295
    renal vascular hypertension, 295
    urinoma, 295
  signs, 296
  staging and x-ray findings, 296*f*–297*f,* 296–297
  symptoms, 296
  treatment
    of complications, 297
    emergency measures, 297
    surgical measures, 297
Klebsiella granulomatis, 251
Klinefelter syndrome, 678*t,* 713, 719
Kock ileal neobladder, 396
KUB film. *See* Plain films, of abdomen

L

Labia majora, 632–633, 756, 777
Labia minora, 632–633, 756, 777
Labial fusion, 660
Laboratory examination, 49–59
  blood clotting studies, 58
  complete blood count, 58
  in elderly, 59*t*
  electrolyte studies, 58
  hormone studies, 59
  patient's age and, 59*t*
  prostate cancer markers, 58
  renal function tests, 57–58
    blood urea nitrogen, 58
    endogenous creatinine clearance, 57–58
    glomerular filtration rate, 57
    serum creatinine, 57
    urine specific gravity, 57
  urethral discharge, 56–57
  urine, 49–56
  urine examination (*See* Urinalysis)
  vaginal exudate, 57
Lactic acid dehydrogenase (LDH), 380–381
Laparoendoscopic single-site surgery (LESS), 150, 174
Laparoscopic pelvic lymph node dissection (LPLND), 156*f*–158*f,* 156–157
Laparoscopy, 149–164
  adrenalectomy, 162–163, 163*f*
  approach to, selection of, 150–151
    hand assistance, 151, 151*f*
    robotic assistance, 151, 152*f*
    transperitoneal vs. retroperitoneal, 151
  complications, 164
    cardiovascular, 149–150
    pulmonary, acid–base, and insufflant-related, 150
  donor nephrectomy, 162
  future perspective, 164
  instrumentation and techniques
    exiting abdomen, 155, 156*f*
    extraperitoneal approach, 154, 156*f*
    instrumentation, 154–155
    obtaining pneumoperitoneum, 152*f,* 152–153, 153*f*
    port placement, 153–154, 154*f,* 155*f*
    postoperative care, 155
    preoperative preparation, 151–152
    video instrumentation and cart, 154
  nephroureterectomy, 160, 161*f*
  orchidopexy, 157–158, 158*f*
  other, 164
  partial nephrectomy, 161*f,* 161–162
  pelvic lymph node dissection, 156*f*–158*f,* 156–157

  - physiology
    - cardiovascular, 149, 150*f*
    - pulmonary, acid–base, and insufflant related, 150
  - pyeloplasty, 162, 162*f*
  - radical cystectomy with urinary diversion, 164
  - radical prostatectomy, 164
  - renal cyst decortication, 158
  - renal mass ablation, 161–162
  - retroperitoneal lymph node dissection, 163*f*, 163–164
  - simple and radical nephrectomy, 158–160, 159*f*, 160*f*
  - varicocelectomy, 157
- Laser probes, for intraureteral lithotripsy, 144
- Lasers, 125–126
- Leiomyomas, 342
  - of epididymis, 385–386
- Leukocyte casts, 53
- Leukocyte esterase test, 51
- Leydig cells
  - age-related changes, 735
  - tumors of, 384
- Light chain deposition disease, 547
- Lipoma, renal, 342
- Lithotrites, 125
- Lower urinary tract
  - hemorrhage of, transcatheter embolization for, 109–110
  - neural control of, 473–474
  - somatic nerve supply to, 473
  - ultrasonography of, 126
- Lower urinary tract dysfunction
  - in Alzheimer disease, 474
  - assessment of, 477–478
  - causes of
    - cauda equina syndrome, 477
    - cerebrovascular accident, 474
    - dementia, 474
    - multiple sclerosis, 475–476
    - multiple system atrophy, 475
    - neurospinal dysraphism, 477
    - Parkinson's disease, 475
    - spinal cord injury, 476
  - management of
    - β_3-adrenoceptor agonists, 479
    - anticholinergics, 478–479
    - behavioral treatments, 478
    - conservative treatments, 478
    - desmopressin, 479
    - neuromodulation, 480
    - onabotulinumtoxin A, 479
    - pharmacotherapy, 478–480
  - physiology of, 473–474
  - urine testing for, 477–478
  - urodynamic studies, 477–478
  - voiding dysfunction management
    - clean intermittent catheterization, 480
    - indwelling catheters, 480
    - reconstructive surgery, 481
    - sphincterotomy, 480–481
- Lower urinary tract symptoms
  - phosphodiesterase type-5 inhibitors for, 505
  - urodynamic evaluations of, 496
- L-Q (linear quadratic) equation, in radiotherapy treatment, 422
- Lung metastases, from Wilms tumor, 344
- Luteinizing hormone (LH), 703, 704
- Luteinizing hormone-releasing hormone (LHRH), 370–371, 645
- Lymphocele, 139
- Lymphogranuloma venereum
  - clinical presentation, 251
  - etiology, 251
  - treatment, 249*t*, 251
- Lymphoma, 385

M

- Macrogenitosomia, 515
- Magnetic resonance angiography (MRA), 96*f*
- Magnetic resonance imaging (MRI), 86
  - advantages and disadvantages, 95, 98
  - angiomyolipoma on, 341
  - clinical applications, 88, 90–91, 95
  - comparison with other methods, 100*f*, 103*f*
  - kidney, 94*f*
  - pelvis, 97*f*
  - principles, 86, 88
  - prostate cancer, 359
  - renal masses on, 332–333
  - Wilms tumor on, 344
- Magnetic resonance urography, 91, 95
- Malakoplakia, 217
- Male genitalia, external
  - development of, 672*f*–673*f*, 673–675, 675*f*–677*f*
  - physical examination, 42–44
- Male sexual dysfunction, 609. *See also* Penile erection
  - ejaculation and, 622
  - emission and, 622
  - erectile dysfunction (*See* Erectile dysfunction [ED])
  - orgasm and, 622
  - premature ejaculation, 622
  - retrograde ejaculation, 622
- Malrotated kidney, 20
- Mammalian target of rapamycin inhibitors
  - disadvantages of, 566
  - for metastatic renal cell carcinoma, 340
  - toxicities of, 409*t*
- Masculinizing (female to male) gender-affirming surgery, 759–766
  - anterior lateral thigh flap for, 761*f*, 761–762, 764–766
  - complications of, 766
  - groin flaps, 761*f*, 762–763, 766
  - metoidioplasty, 759–760, 760*f*
  - neophallus, 764*f*
  - penile prosthetics, 766*f*, 766–767
  - phalloplasty, 760, 760*t*, 763*f*, 765
  - phallo-urethroplasty, 765*f*
  - radial artery forearm flap for, 761, 761*f*, 765–766
  - specialist surgeons in, 764
  - staging of, 763, 763*t*
  - suprapubic flap, 761*f*, 762–763
- Masking, 785
- Massachusetts Male Aging Study, 609
- Matrix calculus, 260
- Maximum urethral closure pressure (MUCP), 488
- Maximum urethral pressure, 488
- Measurement bias, 782
- Meatal cysts, 776*f*
- Meatal stenosis, 656, 775
- Medical exam-induced gender dysphoria, 748
- Medical expulsive therapy (MET), 276
- Medullary cystic disease, 548

- Medullary sponge kidney, 272, 530, 531*f*, 548
- Megacystis, 587
- Megalopenis, 645
- Megameatus, 775
- Meiosis, 706, 707*f*, 707*t*
- Membranoproliferative glomerulonephritis (MPGN)
  - type I, 544
  - type II, 544–545
- Membranous nephropathy, 544
- Mercaptoacetyltriglycine, 187
- Mercaptopropionylglycine (Thiola), 285
- Mesoblastic nephromas, 344
- Mesorchium, 24
- Metastasectomy, 339
- Metastatic bladder cancer, 412
- Metastatic disease
  - adjuvant therapy for, 408
  - neoadjuvant therapy for, 408
  - systemic therapy for, 407–408
- Metastatic hormone-sensitive prostate cancer, 412–413
- Metastatic prostate cancer, 413
- Metastatic renal cell carcinoma
  - bevacizumab for, 340
  - cytoreductive nephrectomy for, 339
  - immune therapy for, 340–341
  - mammalian target of rapamycin inhibitors for, 340
  - metastasectomy for, 339
  - prevalence of, 338–339
  - radiation therapy for, 341
  - risk stratification for, 339
  - surgery for, 339
  - targeted therapy for, 339–340
  - treatment of, 338–341
  - tyrosine kinase inhibitors for, 340
- Metastatic testicular tumors, 385
- Methotrexate, 409*t*
- 17α-Methyl-19-nortestosterone, 744
- Metoidioplasty, 759–760, 760*f*
- Metrifonate, for schistosomiasis, 238
- Metyrapone, for Cushing's syndrome, 515
- Microlaparoscopy, 150
- Micropenis, 645, 646*t*, 695*f*, 695*t*, 695–696, 776
- Micturition, 453
  - neural control, 453, 474*f*–475*f*
    - afferent pathways, 454
    - afferent signaling from urothelium/suburothelium, 454–455
    - of bladder emptying, 455–456
    - of bladder filling, 455
    - parasympathetic pathways, 453–454
    - somatic pathways, 454
    - sympathetic pathways, 454
  - pharmacologic targets
    - adrenergic receptors, 460–462
    - antimuscarinics, 459–460
    - α-ARs, 460
    - β-ARs, 460–461
    - botulinum toxin-sensitive mechanisms, 464–465
    - calcium channels, 462
    - central nervous system, 456–458
    - dopamine mechanisms, 458
    - future perspective, 465
    - GABA mechanisms, 457–458
    - ion channels, 462
    - muscarinic receptors, 458–459
    - NK1 receptor mechanisms, 458
    - noradrenaline mechanisms, 458
    - opioid receptors, 456–457
    - peripheral, 458–465
    - potassium channels, 462
    - serotonin (5-HT) mechanisms, 457
  - physiology of, 489*f*
  - pontine micturition center, 473
- Micturition diary, 501
- Midurethral sling surgery, 500
- Mifepristone, 515
- Mirabegron, 461–462, 479
- Mitomycin C, 317–318
- Mitosis, 706, 706*t*, 707*f*, 707*t*
- Mitotane, for adrenocortical carcinoma, 515
- Mitoxantrone, 409*t*
- Mixed gonadal dysgenesis, 678*t*
- Mixed urinary incontinence (MUI)
  - diagnosis, 505
  - treatment, 505
  - urodynamics for, 495
- Morphine, for detrusor overactivity, 456
- Mucopurulent cervicitis
  - clinical findings of, 246
  - diagnosis and treatment of, 246–247
- Müllerian-inhibiting substance (MIS), 672
- Müller's tubercle, 21, 26
- Multicystic kidney, 522
- Multiple myeloma, kidney diseases in, 547
- Multiple sclerosis (MS), 475–476
- Multiple system atrophy, 475
- Muscarinic receptors, 458–459, 478
- MUSE (medicated urethral system for erection), 619
- *Mycobacterium smegmatis,* 51
- *Mycobacterium tuberculosis,* 229
- *Mycoplasma genitalium,* 244
- Myelomeningocele, 477
- Myotonic dystrophy, 719

N

- National Comprehensive Cancer Network (NCCN), 424, 426
- National Institute of Diabetes and Digestive and Kidney Disease criteria, for interstitial cystitis, 588, 588*t*
- National Kidney Foundation, 557
- National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (K/DOQI), 557
- National Wilms Tumor Study, 342–343
- Natural orifice transluminal endoscopic surgery (NOTES), 150
- *Neisseria gonorrhoeae*
  - description of, 38
  - urethritis caused by, 244
- Neoadjuvant therapy, 408, 411
- Neoclitoris, 754
- Neodymium:YAG lasers, 125–126
- Nephrectomy, laparoscopic, 158–160, 159*f*, 160*f*
- Nephric system
  - anomalies, 20
  - development, 18*f*
  - mesonephros, 17, 18*f*
  - metanephros, 17–18, 18*f*–19*f*
  - pronephros, 17, 18*f*
  - renal and ureteral development, 18–20

- Nephroblastoma. *See* Wilms tumor
- Nephrocalcinosis, 262
- Nephrogenic rests, 343
- Nephrogenic system fibrosis (NSF), 88, 90
- Nephron, 3–4, 5*f*
- Nephroscopes, 135, 135*f*
- Nephroscopy
  - description of, 135*f*–136*f*, 135–136
  - for renal stones, 136*f*, 136–137
- Nephrostomy catheter, 133–135, 134*f*
- Nephrotic syndrome
  - diagnosis, 543–544
  - differential diagnosis, 545
  - diseases associated with
    - focal glomerulosclerosis, 544
    - membranoproliferative glomerulonephritis, 544–545
    - membranous nephropathy, 544
    - minimal glomerular lesions, 544
    - miscellaneous diseases, 545
  - laboratory findings, 545
  - prognosis, 545–546
  - symptoms and signs, 545
  - treatment, 545
- Nephrotoxicity, of contrast agents, 64
- Nephroureterectomy, laparoscopic, 160, 161*f*
- Neuroblastoma, Wilms tumor versus, 344
- Neurogenic bladder
  - assessment of, 477–478
  - causes of
    - cauda equina syndrome, 477
    - cerebrovascular accident, 474
    - dementia, 474
    - multiple sclerosis, 475
    - multiple system atrophy, 475
    - neurospinal dysraphism, 477
    - Parkinson's disease, 475
    - spinal cord injury, 476
  - definition of, 473
  - lower urinary tract neural control, 473–474
  - management of
    - β_3-adrenoceptor agonists, 479
    - anticholinergics, 478–479
    - behavioral treatments, 478
    - conservative treatments, 478
    - desmopressin, 479
    - neuromodulation, 480
    - onabotulinumtoxin A, 479
    - pharmacotherapy, 478–480
  - urine testing for, 477–478
  - urodynamic studies for, 478, 495–496
  - voiding dysfunction management in
    - clean intermittent catheterization, 480
    - indwelling catheters, 480
    - reconstructive surgery, 481
    - sphincterotomy, 480–481
- Neurologic survey, 46
- Neuromodulation, 480
- Neuropathic incontinence, 506
- Neurospinal dysraphism, 477
- Niridazole, for schistosomiasis, 239
- Nitric oxide (NO), 608–609
- Nitrite reductase test, 51
- Nitrofurantoin, for urinary tract infection, 207*t*, 207–208
- Nitroprusside test, 56
- Nivolumab, 420
- NK1 receptor mechanisms, in micturition, 458
- NMP22 BladderChek test, 313
- Nocturia, 36
- Nocturnal penile tumescence (NPT) test, 615
- Nomogram, 359, 361*f*
- Nonarteritic anterior ischemic optic neuropathy (NAION), 618
- Nongonococcal urethritis, 246
- Nonseminomatous germ cell tumors (NSGCTs), 377. *See also* Germ cell tumors
- Noonan syndrome, 719
- Noradrenaline mechanisms, in micturition, 458
- Nuclear magnetic resonance (NMR), 88
- Nuclear matrix protein 22 test, 55

O

- Obesity
  - erectile dysfunction and, 611
  - urinary calculi and, 272
- Obstructed megaureter, 579, 579*f*
- Obstruction and stasis, urinary, 177–188
  - acquired, 177
  - bladder neck obstruction
    - compensation phase, 184
    - decompensation phase, 184–185
  - classification, 177
  - clinical findings
    - imaging, 185–187, 186*f*
    - instrumental examination, 187
    - isotope scanning, 187
    - laboratory findings, 185
    - signs, 185
    - symptoms, 185
  - complications, 187
  - congenital, 177
  - differential diagnosis, 187
  - diverticula, 179
  - etiology, 177
  - kidney, 179, 182, 182*f*–183*f*, 184
  - lower tract, 177
  - midtract
    - compensatory phase, 178*f*, 178–179
    - decompensatory phase, 179
  - pathogenesis and pathology, 177–184
  - prognosis, 188
  - treatment, 187–188
  - upper tract, 179–184
  - ureter, 179, 180*f*–181*f*
- Obstructive uropathy, 546–547
- Oliguria, 37, 551. *See also* Acute kidney injury (AKI)
- Omega–3 fatty acid, in IgA nephropathy, 543
- Onabotulinumtoxin A, 479, 481
- Oncocytomas, renal, 330*f*, 341
- Opioid receptors, in micturition, 456–457
- Orchidopexy, laparoscopic, 157–158, 158*f*
- Orchitis, 220–221
- Orgasm, 622
- Ormond disease, 581
- Ospemifene, 640
- Otis urethrotome, 124
- Outcome, 781
- Ovarian vein varices, transcatheter embolization for, 112
- Overactive bladder syndrome, 504

Overflow incontinence (OI), 37, 505–506
Ovotesticular DSD, 678*t,* 692–693
Oxamniquine, for schistosomiasis, 238–239

P

Paclitaxel, 409*t*
PADUA score, 330, 331*t*
Pain
  epididymal, 35
  local, 31
  prostatic, 35
  referred, 31
  renal, 31–32, 32*f*
  testicular, 35
  ureteral, 32, 32*f*
  vesical, 32, 35
Papillary adenomas, 342
Papillary urothelial neoplasm of low malignant potential (PUNLMP), 311, 316
Paraneoplastic erythrocytosis, 329
Paraneoplastic syndromes, 329
Paranephric abscesses, 212
Paraphimosis, 653, 775
Parasympathetic pathways, micturition, 453–454
Parathyroid hormone-related peptide (PTHrP), 329
Parkinson's disease, 475
Paroxetine, 622
Partial androgen deficiency in the aging male (PADAM), 735
Partial androgen insensitivity syndrome, 681*t,* 688–689
Partial cystectomy, 319
Partial nephrectomy
  laparoscopic, 161*f,* 161–162
  for renal cell carcinoma, 337
  robotic, 173–174
Pasireotide, 515
Patent urachus
  diagnosis, 586
  sign and symptoms, 586, 586*f*
  treatment, 586
Pedal lymphangiography (LAG), 381
Pediatric urology
  appendix testis torsion, 773–774
  balanoposthitis, 775
  digital photography, 778
  epididymis, 773
  epididymoorchitis, 773–774
  foreskin, 774–775, 775*f*
  genital examination in, 770–773
  hydrocele, 772–773
  information gathering in, 769–770
  inguinal canal, 773
  inguinal hernia, 772*f,* 772–773
  interactions with child, 770
  patient interactions in, 769–770
  penis, 773–775
  physical examination in, 770–778
  scrotum, 773
  smegma, 775, 775*f*
  spermatic cord, 773
  testicular torsion, 773–774
  testis, 773
  undescended testis, 771*f*
Pelvic congestion syndrome, transcatheter embolization for, 112
Pelvic floor muscle training, 503
Pelvic fractures, 110
Pelvic hemorrhage transcatheter embolization for, 109–110
Pelvic lipomatosis, 592
Penicillin
  G, for actinomycosis, 235
  for urinary tract infection, 208
Penile erection, 605
  anatomy and hemodynamics of, 606
  centrally originated, 605–606
  central-stimulated, 605–606
  genital-stimulated, 605
  hormones and sexual function, 607
  inducers/inhibitors, 608*t*
  innervation and, 605–606
  mechanism of, 606*f,* 606–607, 608*f*
  neurotransmitters and pharmacology of, 607–608
  phases of, 607*f,* 607*t*
  signal transduction in, 609
  smooth-muscle contraction/relaxation mechanism, 608–609
Penile intraepithelial neoplasia, 386
Penile inversion vaginoplasty, 756
Penile prostheses/prosthetics, 621*t,* 621–622, 766*f,* 766–767
Penile thermal sensory testing, 615
Penile tumors
  differential diagnosis, 387
  epidemiology, 386
  imaging, 387
  laboratory findings, 387
  pathology, 386
  patterns of spread, 386
  prognosis, 388
  risk factors, 386
  signs and symptoms, 387
  treatment, 387–388, 388*f*
  tumor staging, 387, 387*t*
Penile venous surgery, 621
Penis, 42–43
  acquired disorders of
    circumcision, 653
    paraphimosis, 653
    penile phlebothrombosis and lymphatic occlusion, 656
    Peyronie's disease, 623–625, 652
    phimosis, 652–653
    priapism, 625, 651–652
  appearance, 9*f,* 14–15
  blood supply, 15
  congenital anomalies of
    apenia, 645
    megalopenis, 645
    micropenis, 645, 646*t,* 776
  congenital buried, 776, 777*f*
  erectile dysfunction (*See* Erectile dysfunction [ED])
  hidden, 776
  histology, 15
  injuries to, 306
  invasive carcinoma of, 386
  physical examination, 42–43
  size of
    in adults, 645, 646*t*
    in children, 776
  torsion of, 776
Penoscrotal transposition, 774
Peptide hormones, 703

Percutaneous endourology, 129
  antegrade pyelography, 132–133
  aspiration and biopsy, 138–142
    differential diagnosis, 138*t*
    indications, 138*t*
    renal and retroperitoneal tumors, 139–142
    renal biopsy, 139–140
    renal cysts, 138–139
    retroperitoneal fluid collections, 139
  catheter placement, 133–135
  endoscopic intrarenal instrumentation, 135–136
  imaging and puncture techniques, 129–130, 130*f*–131*f*
  nephroscopy, 135–138
  pressure/perfusion studies, 132–133
Percutaneous nephrostomy catheter placement, 133–135, 134*f*
Percutaneous pressure/perfusion study, 132–133, 133*f*
Percutaneous renal access, 129–130, 130*t*
Percutaneous transluminal angioplasty, for fibromuscular dysplasia, 113
Percutaneous urograms, 68, 71
Perineal body, 755*f*
Perineal compression, on penile arteries, 616
Perineal neurovascular bundles, 633
Perinephric abscesses, 212
Peripheral vascular disease, 565
Peritoneal irritation, 35
Persistent cloaca, 24
Persistent genital arousal disorder (PGAD), 637*t*, 639
Persistent Müllerian duct syndrome, 681*t*, 690*f*, 690–691
Peyronie's disease, 43, 623–625, 652
Phallic reconstruction, 701
Phalloplasty, 760, 760*t*, 763*f*, 765
Phallo-urethroplasty, 765*f*
Phimosis, 652–653
Phosphate supplementation, 284
Phosphodiesterase type-5 inhibitors (PDE-5Is), 605, 616–619
  action mechanism, 617–618
  adverse events, 618
  clinical efficacy, 618
  lower urinary tract symptoms treated with, 505
  period of efficacy, 618
  time of onset, 618
  warnings and drug interaction, 618
Phosphorus defects, 548
Physical examination, of genitourinary tract
  bladder, 42
  female genitalia, 44
    vaginal, 44
  kidneys, 41–42
    auscultation, 42
    inspection, 41
    palpation, 41, 42*f*
    percussion, 41
    transillumination, 41–42
  male genitalia, external
    epididymis, 43
    penis, 42–43
    scrotum, 43
    spermatic cord, and vas deferens, 43
    testes, 43
    testicular tunics, and adnexa, 43–44
  neurologic survey, 46
  rectal examination, male
    lymph nodes, 46
    prostate, 44–46
    seminal vesicles, 46
    sphincter, and lower rectum, 44
Phytotherapy, for BPH, 598
PICO, 789–791
Pili, 203
Pituitary insufficiency, and infertility, 717
Placental alkaline phosphatase (PLAP), 381
Plain films, of abdomen, 64, 65*f*–66*f*
Pneumatic probes, 144
Pneumaturia, 37
Polycystic kidney disease, 547–548, 548*t*
Polycythemia, 742
Pontine micturition center, 473
Postcaval ureter. *See* Retrocaval ureter
Postembolization syndrome (PES), 110, 112
Posterior urethral valves, 646, 647*f*
  instrumental examination, 648
  laboratory findings, 646
  prognosis, 649
  symptoms and signs, 646
  treatment, 648–649
  ultrasonography, 648
  x-ray findings, 646, 648
Poststreptococcal glomerulonephritis, 542–543
Postvoid residual (PVR), 485–486
Potassium channels, in micturition, 462
Potassium citrate, 284
Potassium wastage syndrome, 549
Power mode Doppler, 77
Prader orchidometer, for measuring testicular volume, 709, 710*f*
Prader–Willi syndrome, 717
Praziquantel, for schistosomiasis, 238
Preclinical studies, 785
Pregnancy
  antibiotics effect on, 222*t*
  sexual activity during, 634
  urinary tract infection in, 221–222, 222*t*
Preimplantation genetic diagnosis, 731
Premature ejaculation, 609, 622
Preputial calculi, 287
Preputial stones, 287
Priapism, 625, 651–652
  high-flow
    description of, 652
    transcatheter embolization for, 112
  ischemic, 652
  low-flow, 652
Primary hematuria, 543
Probiotics, for urinary tract infection, 209
Progesterone, 687
Programmed cell death 1 (PD-1), 415–417
Programmed death-1, 340
Progression-free survival, 407
Prolapse of female urethra, 663
Pronephric duct, 26
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, 364
Prostate abscess, 219, 220*f*
Prostate acid phosphatase (PAP), 418
Prostate artery embolization (PAE), for benign prostatic hyperplasia, 107–109, 109*f*

- Prostate cancer
  - biomarkers of, 363
  - castration-resistant, 413
  - checkpoint inhibitors for, 419
  - chemoprevention, 364–365
  - clinical findings
    - laboratory findings, 355
    - signs, 355
    - symptoms, 355
    - tumor markers, 355–357
  - diagnosis and evaluation
    - axial imaging, 359
    - bone scan, 359
    - endorectal MRI, 359
    - grading and staging, 358, 358*t*
    - prostate biopsy, 357
    - TRUS, 358–359
  - epidemiology, 351–352
  - immunotherapy for, 418–419
  - incidence, 351–352
  - localized, treatment of, 365–369
    - active surveillance, 366
    - brachytherapy, 368
    - cryosurgery, 368–369
    - external beam therapy, 367–368
    - focal therapy, 369
    - general considerations, 365
    - radical prostatectomy, 366–367
    - watchful waiting, 365–366
  - metastatic, treatment of, 370–372
    - endocrine therapy, 370, 370*t*
    - luteinizing hormone-releasing hormone, 370–371
  - metastatic hormone-sensitive, 412–413
  - molecular genetics and pathobiology, 354–355
  - multivariable risk assessment, 360–362
    - CAPRA score, 362, 362*f*
    - lookup tables and nomograms, 361*f*, 361–362
    - risk groups, 360–361
  - pathology, 352–354
  - radiotherapy, 423–430
    - brachytherapy, 427–428
    - complications, 429–430
    - conventional EBRT, 425
    - 3D conformal radiotherapy, 425
    - dose escalation radiotherapy, 426
    - hormonal therapy and, 428
    - intensity-modulated radiotherapy, 425
    - particle beam radiation, 428
    - postoperative, 428–429
  - recurrent, treatment of, 369–370
    - following radiation therapy, 370
    - following radical prostatectomy, 369–370
  - screening, 363–364
  - testosterone levels and, 742–743
  - tests, 55–56
  - in transgender women, 759
  - vaccines, 418–419
- Prostate cancer antigen 3 (PCA3), 55, 356
- Prostate Cancer Prevention Trial (PCPT) study, 355–356
- Prostate disorders
  - calculi, 599*f*–600*f*, 599–600
  - cysts, 599–600
- Prostate gland, 593
  - anatomy, 7*f*, 8–10, 9*f*, 12*f*
  - blood supply, 12
  - histology, 10, 11*f*, 12
  - lymphatics, 12
  - neoplasms of, 593 (*See also* Prostate cancer)
    - benign prostatic hyperplasia, 593–599
    - carcinoma of prostate, 351–372 (*See also* Prostate cancer)
  - nerve supply, 12
  - relations of, to other organ, 9*f*–10*f*, 10
- Prostate-specific antigen (PSA)
  - cancer detection uses of, 355–356
  - density, 356
  - isoforms, 356
  - kinetics, 356
  - normal, 355
  - PCA3, 356
- Prostatic balloon dilatation, 125
- Prostatic calculi, 287
- Prostatic intraepithelial neoplasia (PIN), 353
- Prostatic nodules, 45, 45*f*
- Prostatitis, 222
- Prostatomembranous urethra, 9*f*
- ProstaVax, 418
- Proteinuria, 539
- Pseudoaneurysms, transcatheter embolization for, 107, 108*f*
- Pseudohermaphrodites
  - female, 680*t*, 685–687
  - male, 680*t*–681*t*, 687–689
- Psychosexual therapy, for erectile dysfunction, 616
- P2X3 receptors, 462–463
- P2X3-receptor antagonists, 462–463
- Pyelonephritis, 403
  - chronic, 211*f*, 211–212
  - vesicoureteral reflux and, 195
- Pyeloplasty
  - laparoscopic, 162, 162*f*
  - robotic, 172–173
- Pyonephrosis, 215*f*, 215–216, 270
- Pyuria, 51

R

- Radial artery forearm flap phallourethroplasty, 761, 761*f*, 765–766
- Radiation therapy. *See also* Radiotherapy
  - for metastatic renal cell carcinoma, 341
  - for prostate cancer, 367–368
  - for testicular seminoma, 438–439
  - for Wilms tumor, 345
- Radiation Therapy Oncology Group (RTOG), 424
- Radical cystectomy
  - description of, 319
  - laparoscopic, 164
    - robotic, 171–172
- Radical nephrectomy, for renal cell carcinoma, 336*f*, 336–337
- Radical prostatectomy, laparoscopic
  - description of, 164
  - prostate cancer treated with, 366–367
  - robotic-assisted, 169–171, 170*t*–172*t*
- Radicular pain, 42
- Radiculitis, 42
- Radiofrequency ablation (RFA), for small renal masses, 141
- Radiographic tomography, 65, 68*f*
- Radiography, 63
  - advantages and disadvantages, 64
  - angiography, 71, 74, 80*f*–81*f*

  cystography and cystourethrography, 71, 71*f*–75*f*
  equipment and techniques
    adverse reactions, 64
    contrast media, 63–64
    image intensification, 63
    image recording, 63
    radiography fluoroscopy, 63
  lymphangiography, 71
  plain films, abdomen, 64, 65*f*–66*f*
  urethrography, 71, 76*f*–78*f*
  urography, 64–65, 67*f*–70*f*, 68, 71
  vasography, 71, 79*f*
Radiology, 63
  comparison of methods, 98–99
  computed tomography, 81–86 (*See also* Computed tomography [CT])
  magnetic resonance imaging, 86–98 (*See also* Magnetic resonance imaging [MRI])
  radiography, 63–74 (*See also* Radiography)
  sonography, 74–81 (*See also* Ultrasound)
  vascular interventional (*See* Vascular interventional radiology)
Radiotherapy, 421–439. *See also* Radiation therapy
  bladder cancer treated with, 319, 430–433
    combined modality therapy, 431–432, 432*t*
    EBRT management, 430–431
    improving treatment outcomes, 432–433
    toxicity, 433
  conventional fractionation, 421
  female urethra cancer treated with, 434
  general principles
    altered fractionation schedules, 422
    brachytherapy, 422–423, 423*f*
    dose per fraction considerations, 422
    mechanisms of cytotoxicity, 421
    radiation sensitivity and tolerance, 421–422
  germ cell tumors treated with, 435–438
  penile cancer treated with, 434–435
  prostate cancer treated with, 423–430
    brachytherapy, 427–428
    complications, 429–430
    conventional EBRT, 425
    3D conformal radiotherapy, 425
    dose escalation radiotherapy, 426
    hormonal therapy and, 428
    intensity-modulated radiotherapy, 425
    particle beam radiation, 428
    postoperative, 428–429
  renal cell carcinoma treated with, 433
  testicular cancer treated with, 435
  urethral cancer treated with, 434–435
  urinary tract tumors treated with, 430
Randomized controlled trials (RCTs)
  adherence, 787–788
  description of, 785
  duration of, 787
  examples of, 790*t*
  interpretation caveats for, 787–788
  study population for, 787
  timing of, 787
Rapidly progressive glomerulonephritis, 543
Recall bias, 784
Red diaper syndrome, 50
5α-reductase inhibitor, for BPH, 597
5α-reductase type 2 deficiency, 681*t*, 689*f*–690*f*, 689–690
Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, 357
Reflux nephropathy, 195
Renal abscess
  management, 212
  presentation and findings, 212
  radiographic imaging, 212, 213*f*
  signs and symptoms of, 334
Renal adenocarcinoma, clear cell, 330*f*
Renal agenesis, 521
Renal and ureteral stones, 259–285
  calcium, 262–265
  with caliceal diverticula, 273, 273*f*
  in children, 273
  crystal component of, 260
  cystine, 266*f*, 266–267
  in dysmorphia, 272, 272*f*
  etiology of, 259–260, 260*f*
  evaluation of
    differential diagnosis, 273–274
    history, 274
    physical examination, 275
    risk factors, 274–275
  indinavir, 267
  intervention
    conservative observation, 276
    dissolution agents, 277–278
    extracorporeal shockwave lithotripsy, 278*f*, 278–282
      intraoperative considerations, 281–282
      postoperative care, 282, 282*f*
      preoperative evaluation, 281
      shockwave physics, 279*f*, 279–281
    obstruction, relief of, 278
    open-stone surgery, 283
    partial nephrectomy, 283
    percutaneous nephrolithotomy, 283
    ureterolithotomy, 283
    ureteroscopic stone extraction, 282–283
  matrix component of, 260
  in medullary sponge kidney, 272
  obesity and, 272
  pregnancy and, 271*f*, 271–272
  prevention of, 283–284
    metabolic evaluation, 284
    oral medications, 284–285
  radiologic investigations
    computed tomography, 275
    magnetic resonance imaging, 276
    nuclear scintigraphic, 276, 277*f*
    pyelography, 275–276, 276*f*
    retrograde pyelography, 276
    tomography, 275–276
  in renal malformations, 273, 274*f*
  in renal transplantation, 271, 271*f*
  renal tubular acidosis and, 272–273
  silicate, 267
  struvite, 265–266, 266*f*
  symptoms and signs of
    fever, 270–271
    hematuria, 270
    infection, 270, 270*f*
    nausea and vomiting, 271
    pain, 267–270, 268*f*
    tumors and, 273

Renal and ureteral stones (*Cont.*):
  uric acid, 266
  urinary ions
    calcium, 261
    citrate, 262
    magnesium, 262
    oxalate, 261
    phosphate, 261
    sodium, 261–262
    sulfates, 262
    uric acid, 261, 262*f*
  xanthine, 267
Renal artery
  aberrant, 531
  aneurysms, transcatheter embolization of, 114
  embolization of, 112, 337
  stenosis of, 112–113, 114*f*, 569
  stenting of, 112–114, 114*f*
Renal biopsy, 139–140, 540–541
Renal cell carcinoma (RCC)
  computed tomography of, 331, 332*f*
  differential diagnosis of, 333–334
  disseminated
    bevacizumab for, 340
    cytoreductive nephrectomy for, 339
    immune therapy for, 340–341
    mammalian target of rapamycin inhibitors for, 340
    metastasectomy for, 339
    prevalence of, 338–339
    radiation therapy for, 341
    risk stratification for, 339
    surgery for, 339
    targeted therapy for, 339–340
    treatment of, 338–341
    tyrosine kinase inhibitors for, 340
  epidemiology of, 334
  etiology of, 334
  hereditary forms of, 334–335
  histologic findings, 334
  hypercalcemia associated with, 329
  incidence of, 329
  localized
    adjuvant treatment of, 338
    follow-up care for, 338
    treatment of, 336–338
  magnetic resonance imaging of, 95*f*–96*f*, 333, 333*f*
  metastatic
    bevacizumab for, 340
    chemotherapy for, 412
    cytoreductive nephrectomy for, 339
    immune therapy for, 340–341
    mammalian target of rapamycin inhibitors for, 340
    metastasectomy for, 339
    prevalence of, 338–339
    radiation therapy for, 341
    risk stratification for, 339
    surgery for, 339
    targeted therapy for, 339–340
    treatment of, 338–341
    tyrosine kinase inhibitors for, 340, 412
  paraneoplastic erythrocytosis caused by, 329
  paraneoplastic syndromes associated with, 329
  pathogenesis of, 335
  pathology associated with, 334
  positron emission tomography of, 333
  risk factors for, 334
  staging of, 335*t*, 335–336
  subtypes of, 334
  succinate dehydrogenase, 335
  TNM staging of, 335*t*, 335–336
  transcatheter embolization for, 110*f*, 110–111
  treatment of
    active surveillance as, 336
    adjuvant, 412
    checkpoint inhibitors in, 417
    disseminated disease, 338–341
    external beam radiation therapy, 433
    follow-up care, 338
    immunotherapy, 419–420
    localized disease, 336–338
    partial nephrectomy, 337
    radical nephrectomy, 336*f*, 336–337
    surgical resection, 336–338
  vena caval tumor thrombus associated with, 338*f*
  von Hippel–Lindau disease and, 334–335
Renal cysts, 138–139, 523, 524*f*, 525–527
  Bosniak classification of, 330, 330*t*, 526
  clinical findings, 526–527
  complications, 527
  differential diagnosis, 527
  etiology and pathogenesis, 526
  pathology, 526
  prognosis, 527
  simple, 333
  treatment, 527
  ultrasonography of, 331, 332*f*
Renal denervation, 114
Renal diabetes insipidus, 549
Renal dysplasia, 522
Renal function
  cessation of, with transcatheter embolization, 111–112
  laboratory tests of, 57–58
    blood urea nitrogen, 58
    endogenous creatinine clearance, 57–58
    glomerular filtration rate, 57
    serum creatinine, 57
    urine specific gravity, 57
  measurement of, 478
Renal fusion, 528
  clinical findings, 528
  complications, 530
  differential diagnosis, 528, 530
  etiology and pathogenesis, 528
  pathology, 528, 529*f*
  prognosis, 530
  treatment, 530
Renal glycosuria, 548–549
Renal hamartoma. *See* Angiomyolipoma (AMLs)
Renal hypercalciuric nephrolithiasis, 264
Renal infarcts, 532–533
Renal lipomas, 342
Renal masses
  biopsy of, 333
  Bosniak classification for, 330–331, 331*t*
  clinical presentation of, 329–330
  computed tomography of, 330*f*, 330–331, 331, 332*f*
  differential diagnosis of, 333–334
  epidemiology of, 329

  - imaging classification for, 330–331, 331*t*
  - laboratory findings in, 329–330
  - magnetic resonance imaging of, 332–333
  - PADUA score for, 330, 331*t*
  - paraneoplastic syndromes associated with, 329
  - positron emission tomography of, 333
  - radiographic findings, 330, 330*f*
  - radionuclide imaging of, 333
  - RENAL nephrometry score for, 330, 331*t*
  - signs and symptoms of, 329
  - small, 336
  - treatment of
    - active surveillance as, 336
    - localized disease, 336–338
    - surgical resection, 336–338
    - thermal ablation, 336
  - ultrasonography of, 330–331, 332*f*
- RENAL nephrometry score, 330, 331*t*
- Renal oncocytoma, 330*f*, 341
- Renal parenchymal neoplasms
  - adenocarcinomas (*See* Renal cell carcinoma [RCC])
  - angiomyolipomas (*See* Angiomyolipoma [AMLs])
  - benign, 341–342
  - hemangiomas, 342
  - juxtaglomerular cell tumor, 342
  - leiomyomas, 342
  - nephroblastoma (*See* Wilms tumor)
  - papillary adenomas, 342
  - renal lipomas, 342
  - renal masses (*See* Renal masses)
  - renal oncocytoma, 341
  - secondary, 346
  - Wilms tumor (*See* Wilms tumor)
- Renal pelvic and ureteral carcinomas
  - clinical findings
    - imaging, 322–323, 323*f*
    - laboratory findings, 322
    - symptoms and signs, 322
    - ureteropyeloscopy, 323
  - etiology, 321
  - incidence, 321
  - pathology, 321
  - staging and natural history, 321–322, 322*t*
  - treatment, 323–324
- Renal transplantation, 561–562
  - advantage of, 561
  - antibiotic prophylaxis before, 567
  - candidates
    - evaluation of, 563–566, 564*t*–565*t*
    - list of, 561*f*
  - complications of, 568–570
  - cytomegalovirus antibody levels before, 564
  - deceased renal donors for, 567
  - description of, 563
  - disadvantage of, 561
  - expected posttransplant survival score for, 563
  - immunization recommendations for, 564
  - life expectancy calculation, 565–566
  - living renal donors for, 566–567
  - malignancy and, 564–565
  - postoperative care for, 568
  - recipient
    - operation for, 567–568
    - selection of, 567
  - rejection after, 568
  - renal calculi after, 569
  - urinary tract evaluation, 565*t*
  - urinary tract infection after, 569
- Renal tuberculosis, 234. *See also* Tuberculosis
- Renal vein thrombosis, 533, 533*f*
- Renal/retroperitoneal tumors, percutaneous aspiration biopsy of, 139–142, 140*f*
- Renoalimentary fistula, 534, 534*f*
- Renobronchial fistulas, 534
- Renointestinal reflexes, 35
- Resectoscopes, 123, 124*f*
- Resorptive hypercalciuric nephrolithiasis, 264
- Responsiveness, 407
- Retarded ejaculation, 609
- Ret/GDNF signaling pathway, 19
- Retrocaval ureter, 575, 576*f*
- Retrograde ejaculation, 609, 622
- Retrograde endopyelotomy, 123
- Retrograde instrumentation, urinary tract, 117–126
  - cystoscopy, 119–120
  - lasers, 125–126
  - lower tract calculi removal, 125
  - transurethral surgery, 123–125, 124*f*
  - ultrasonography, 126, 126*f*
  - ureteral catheterization, 120*f*–122*f*, 120–123
  - urethral catheterization, 117–118, 119*f*
  - urethroscopy, 119
- Retrograde urography, 68, 69*f*–70*f*
- Retroperitoneal fibrosis, 581*f*, 581–582
- Retroperitoneal fluid collections, 139
- Retroperitoneal lymph node dissection (RPLND), 163*f*, 163–164, 382
- Robotic surgery, 151, 152*f*, 167–174
  - cost-effectiveness, 174
  - da Vinci surgical system, 167–169, 168*f*–169*f*
  - developmental history of, 167
    - AESOP, 167
    - PROBOT, 167
    - ZEUS surgical system, 167
  - future guidelines, 174
  - lower urinary tract operations
    - radical cystectomy, 171–172
    - radical prostatectomy, 169–171, 170*t*–172*t*
  - partial nephrectomy, 173–174
  - pediatric operations, 174
  - single-site, 174

S

- Sacral dimples, 778
- Salvage radiotherapy, 429
- Schistosomiasis
  - clinical findings
    - cystoscopic examination of, 236
    - diagnosis of, 236
    - signs of, 236
    - symptoms of, 236
    - x-ray findings, 236, 237*f*, 238*f*
  - differential diagnosis of, 237
  - etiology of, 235
  - pathogenesis of, 235–236
  - pathology of, 236
  - prognosis, 239

Schistosomiasis (*Cont.*):
  treatment of, 237–239
    antibiotics/urinary antiseptics, 239
    complications of, 239
    medical measures for, 237–238
Schistosomules, 235
Scrotal pain, 773
Scrotal skin graft, 757
Scrotal ultrasound, for male infertility evaluation, 714, 714*f*
Scrotoplasty, 760
Scrotum
  appearance, 14
  blood supply, 14
  histology, 14
  injuries to, 306
  lymphatics, 14
  pediatric, 773
  physical examination, 43
  tumors of, 389
Selection bias, 782
Selective androgen receptor modulators (SARMs), 744
Selective estrogen receptor modulators (SERMs), 744
SelectMDx, 56, 356–357
Self-retaining port, 153*f*
Semen analysis, for male infertility evaluation, 710–712, 711*t*
  computer-assisted, 711
  semen collection, 710–711
  semen leukocyte analysis, 711*t,* 711–712
  sperm morphology, 711
  sperm motility, 711
Semen culture, for male infertility evaluation, 714
Seminal fructose testing, 712
Seminal vesicles
  anomalies of, 600
  appearance, 7*f,* 9*f,* 12
  blood supply, 13
  histology, 12
  lymphatics, 13
  magnetic resonance imaging of, 98*f*
  nerve supply, 13
  stones, 285–286
Seminiferous tubules, 9*f*
Seminoma, 377, 378. *See also* Germ cell tumors
Serlopitant, 458
Serotonin (5-HT), in micturition, 457
Serratia marcescens, 50
Sertoli cells
  description of, 671, 672, 705, 706*f*
  tumors of, 384
Sertoli-cell-only syndrome, 719–720
Serum creatinine, 57
Sex hormone–binding globulin (SHBG), 705
Sexual assault, 635
Sexual differentiation
  chromosomal sex, 671
  disorders involving
    chromosomal sex, 676, 678*t*
    gonadal sex, 676, 679*t*
    phenotypic sex, 676, 680*t*–681*t*
  female genitalia development, 673
  gonadal differentiation, 671–672, 672*f*
  hormones and, 672*f*–673*f,* 672–673
  male genitalia development, 672*f*–673*f,* 673–675, 675*f*–677*f*
Sexual dysfunction
  female (*See* Female sexual dysfunction)
  male (*See* Male sexual dysfunction)
Sexual identity, 747
Sexual pain disorders, 637*t,* 640
Sexual wellness, 631, 633–635
Sexually transmitted infections (STIs), 243–255, 244*t*
  cervicitis, 246–247
  epididymitis, 247*t,* 247–248
  genital ulcer, 248–253, 249*t,* 252*t*
  gonococcal infection, 245
  HIV infection, 253–254
  nongonococcal urethritis, 246
  subclinical human papillomavirus infection, 253
  urethritis, 244–246
Shallow-depth vaginoplasty, 753
Shy–Drager syndrome, 475
Sildenafil (Viagra). *See* Phosphodiesterase type-5 inhibitors (PDE-5Is)
Simple prostatectomy, for BPH, 598–599
Sipuleucel-T, 418
Sirolimus, 566
Sleep apnea, testosterone therapy and, 743
Smegma, 775, 775*f*
Smoking
  bladder cancer and, 309–310
  erectile dysfunction and, 611
Sodium fluoride, 360
Solabegron, 462
Solitary kidney, 20
Solubility product, 259
Somatic pathways, micturition, 454
Somatic storage reflex, micturition, 455
Sonography. *See* Ultrasound
Spectral Doppler, 77
Sperm DNA fragmentation assay, 712
Sperm penetration assay, 712
Sperm retrieval techniques, 727*t,* 727–728
  testis sperm retrieval, 728
  vasal aspiration, 727
Spermatic cord
  appearance, 9*f,* 13
  blood supply, 13
  histology, 13
  lymphatics, 13
  pediatric, 773
  physical examination, 43
  tumors, 386
Spermatogenesis, 705–707
  genetics of, 706, 706*t,* 707*f*
  germ cells and, 705–706, 706*f*
  Sertoli cells and, 705, 706*f*
  sperm maturation, 707
  spermiogenesis, 707
  stages of, 706
Spermiogenesis, 707
Sphincterotomy, 480–481
Spina bifida, 477
Spina bifida cystica, 477
Spinal cord injury, 476
Spinal shock, 476
Spironolactone (Aldactone), 518
Squamous cell carcinoma, of bladder, 312
Statistical significance, 788–789, 789*t*

Step system ports, 154, 155*f*
Stereotactic body radiotherapy (SBRT), 427
Sterility, 27
Steroid hormones, 703
Steroidogenic acute regulatory protein (StAR), 671
Stoma, 401–402, 402*t*
Streptozyme test, 542
Stress urinary incontinence (SUI), 37, 500*f*–502*f*, 500–504
  anatomy associated with, 500*f*–502*f*, 500–501
  causes, 500
  definition, 500
  diagnosis, 501–502
  surgical treatment, 503–504
  treatment, 503–504
  urodynamic characteristics of
    abdominal leak point pressure, 503
    description of, 495
    functional urethral length, 503
    response to bladder distention and change in position, 503
    urethral pressure profile, 502
Striant, 617
Stroke, 474
Subureteric transurethral injection (STING), 197
Succinate dehydrogenase kidney cancer (SDH-RCC), 335
Superficial trigone, 191, 192*f*
Supernumerary gonads, 26
Supernumerary kidneys, 20, 522
Supersonic emitters, 279
Suprapubic flap, 761*f*, 762–763
Suprapubic ultrasound, 126
Swyer's syndrome, 691
Sympathetic pathways, micturition, 454
Sympathetic storage reflex, micturition, 455
Synaptosome-associated protein 25, 479
Syphilis
  clinical presentation of, 249–250
  diagnosis of, 250
  treatment of, 249*t*, 250
Systemic therapy
  as adjuvant therapy, 408
  agents used in, 408–409, 409*t*
  curative, 407–408
  incurable metastatic cancer treated with, 408
  metastatic disease treated with, 407–408
  principles of, 407–410
  surgery and, 408

T

T pouch, 396, 397*f*
Tadalafil (Cialis). *See* Phosphodiesterase type-5 inhibitors (PDE-5Is)
Tamm–Horsfall glycoprotein (THG), 202
Taxotere. *See* Docetaxel
Tc 99m diethylenetriaminepentaacetic acid (DTPA), 187
Tension pneumoperitoneum, 149
Tension-free vaginal tape (TVT), 503
Teratomas, 379
Terazosin, for BPH, 597
Testicular seminoma, 438–439
Testicular sperm extraction (TESE), 728
Testicular torsion, 773–774
Testim topical gel, 616–617
Testis, 13–14, 705
  anatomy, 13–14
  biopsy, for male infertility evaluation, 715–716
  blood supply, 14
  endocrine, 705
  exocrine, 705
  histology, 9*f*, 14
  injuries to, 306
  lymphatics, 14
  magnetic resonance imaging of, 99*f*
  physical examination, 43
Testis cancer markers, 58–59
Testoderm TTS, 616
Testopel subcutaneous pellets, 617
Testosterone
  deficiency of, in older men, 735
  description of, 607, 672, 703, 705, 729
  replacement of, 616–617
    adverse effects of, 617
Thermal ablation, for renal masses, 336
Thin-membrane disease, 547
Thiotepa, 317
Thorotrast, 321
Thrombolysis, catheter-directed, 115
Thrombosis of renal vein, 533, 533*f*
Tissue plasminogen activator, 115
TMPRSS2: ERG, 55
TNM staging, of renal cell carcinoma, 335*t*, 335–336
Torsion, 721
Total bilateral adrenalectomy, 514
Trabeculation, of bladder wall, 178
Tramadol, for detrusor overactivity, 456–457
Transcatheter embolization
  for angiomyolipoma, 111, 111*f*
  for benign prostatic hyperplasia, 107–109, 109*f*
  for bleeding sites, 107
  for high-flow priapism, 112
  for lower urinary tract hemorrhage, 109–110
  for ovarian vein varices, 112
  for pelvic congestion syndrome, 112
  for pelvic hemorrhage, 109–110
  for pseudoaneurysms, 107, 108*f*
  for renal artery aneurysms, 114
  for renal AVFs and malformations, 107
  for renal cell carcinoma, 110*f*, 110–111
  for renal function cessation, 111–112
  for varicocele, 112
Transcytoscopic urethroplasty, 125
Transducers, 77
Transgender patients
  cultural sensitivity/insensitivity, 748
  epidemiology of, 748–749
  feminizing (male to female) gender-affirming surgery, 750–759
    bilateral orchiectomy in, 751, 751*t*
    complications of, 758–759
    criteria for, 750, 750*t*
    definition of, 748
    description of, 749–750
    types of, 749*t*
    vaginal canal, 756–758
    vaginoplasty, 751–756, 753*t*–754*t*, 755*f*–758*f*
  gender pronouns with, 748
  masculinizing (female to male) gender-affirming surgery, 759–766
    anterior lateral thigh flap for, 761*f*, 761–762, 764–766
    complications of, 766

Transgender patients, masculinizing (female to male) gender-affirming surgery (*Cont.*):
    groin flaps, 761*f,* 762–763, 766
    metoidioplasty, 759–760, 760*f*
    neophallus, 764*f*
    penile prosthetics, 766*f,* 766–767
    phalloplasty, 760, 760*t,* 763*f,* 765
    phallo-urethroplasty, 765*f*
    radial artery forearm flap for, 761, 761*f,* 765–766
    specialist surgeons in, 764
    staging of, 763, 763*t*
    suprapubic flap, 761*f,* 762–763
  misgendering of, 748
  terminology associated with, 747–748
Transitional cell carcinoma (TCC)
  checkpoint inhibitors for, 417
  chemotherapy for, 411–412
Transrectal ultrasound (TRUS)
  for male infertility evaluation, 714, 715*f*
  for prostate cancer, 358–359
  for prostate evaluations, 126
Transsexual, 748
Transsphenoidal resection, for Cushing's disease, 514
Transurethral incision of the prostate, for BPH, 598
Transurethral microwave thermotherapy, for BPH, 599
Transurethral resection of ejaculatory ducts (TURED), 726, 726*f*
Transurethral resection of the prostate (TURP)
  for benign prostate hyperplasia, 108, 598
  description of, 124
Transurethral resection of visible bladder tumor (TURBT), 419
Transurethral resection syndrome, 125, 598
Transurethral resection (TUR), 318
Transurethral surgery, 123–125, 124*f*
Transurethral vaporization of the prostate (TUVP), for BPH, 598
Transvestite, 748
Trauma, to testis, 721–722
Trazodone, 619
Treponema pallidum, 249
Trichomonas vaginalis, 246, 714
Trimethoprim–sulfamethoxazole (TMP–SMX), for urinary tract infection, 206*t,* 206–207, 207*t*
Trimix, for ICI, 620
True hermaphroditism. *See* Ovotesticular DSD
True incontinence, 37
Tuberculosis, 229–234, 230*f,* 233*f*
  anticholinergic medications, 234
  clinical findings, 231–233
    cystoscopic examination of, 233
    diagnosis, 231
    laboratory findings, 232
    signs, 232
    symptoms, 232
    x-ray findings, 232, 233*f*
  complications, 234
  differential diagnosis, 233–234
  epididymal infection, 233–234
  etiology, 229
  pathogenesis, 229–231, 230*f*
  pathology of, 231
  renal tuberculosis, 234
Tuberous sclerosis, 335, 341, 523
Tunica albuginea, 633
Turner's syndrome, 678*t,* 691
Tyrosine kinase inhibitors
  checkpoint inhibitors and, 420
  metastatic renal cell carcinoma treated with, 340, 412
  toxicities of, 409*t*

U

Ultrasound, 74, 77, 82*f*–86*f*
  advantages and disadvantages, 81
  bladder, 79
  clinical applications, 77, 79, 81
  Doppler, 79
  kidney, 82*f*
  lower urinary tract applications of, 126
  for percutaneous puncture, 129
  principles, 74, 77
  renal, 77, 79
  renal access guided using, 130–131, 131*f*
  renal calculus, 83*f*
  renal neoplasms, 83*f*
  suprapubic, 126
  of testis and scrotum, 79, 81
  transrectal, 85*f*
Undescended testis, 771*f*
Undifferentiated carcinoma, of bladder, 312
Upper urinary tract dilatation, 579–580, 580*f*
Uprima, 619
Urachal cyst, 24
Urachal diverticulum, 24
Urachal fistula, 24
Ureaplasma urealyticum, 661, 714
Urease inhibitor, for calculi prevention, 285
Ureter, 7, 571
Ureter disorders, 571
  acquired, 580–582
    extrinsic ureteral obstruction, 580–581
    intrinsic ureteral obstruction, 580
    retroperitoneal fibrosis, 581*f,* 581–582
    ureteral obstruction secondary to malignant disease, 582
  congenital, 571–580
    duplication of ureter, 571–572, 572*f*
    ectopic ureter, 575, 575*f*
    obstructed megaureter, 579
    position abnormalities, 575, 576*f*
    upper urinary tract dilatation, 579–580, 580*f*
    ureteral atresia, 571
    ureterocele, 572–574, 573*f*–574*f*
    ureteropelvic junction obstruction, 576*f,* 576–579, 577*f*
Ureteral atresia, 571
Ureteral catheterization
  balloon dilators used in, 123
  brush biopsy using, 120, 120*f*
  catheters for, 121
  double-J catheters for, 122
  guidewire passage used in, 121–122, 122*f*
  indications for, 120–121
  stents, 122–123
  technique for, 121–122, 122*f*
  ureteroscope passage in, 123
Ureteral injury, 298–299
  clinical findings, 298–299
    imaging findings, 298*f,* 298–299
    laboratory findings, 298
    radionuclide scanning, 299

    signs, 298
    symptoms, 298
    ultrasonography, 299
  complications, 299
  differential diagnosis, 299
  etiology, 298
  pathogenesis and pathology, 298
  prognosis, 299
  treatment, 299
Ureteral obstruction
  extrinsic, 580–581
  intrinsic, 580
Ureteral stones, ureterorenoscopy for, 143–144. *See also* Renal and ureteral stones
Ureteral strictures, ureterorenoscopy for, 144–145
Ureteral tuberculosis, 234. *See also* Tuberculosis
Ureteral tumors, 145
Ureterocele, 20, 572–574, 573*f*
  clinical findings, 574
  treatment, 574
  ultrasound, 574, 574*f*
Ureteropelvic junction obstruction
  causes, 576–577
  clinical findings, 576*f*, 577
  diagnosis, 577, 577*f*
  minimally invasive surgery for, 579
  surgery for, 577–579
Ureteropelvic stenosis
  treatment of, 137
  ureterorenoscopy for, 144
Ureteropyeloscopy, 323
Ureterorenoscopy, 129, 142*f*, 142–145
  diagnostic, 143
  indications for, 142*t*
  instruments, 142, 142*f*
  for ureteral stones, 143–144
  for ureteral strictures, 144–145
  for ureteral tumors, 145
  for ureteropelvic stenosis, 144
Ureterosigmoidostomy, 396, 396*f*
Ureterotrigonal complex, 192*f*
Ureterovesical junction, 191
  anatomy, 191–192, 192*f*
    endodermal component, 191–192
    mesodermal component, 191
  physiology, 192, 193*f*
  repair of, 197
Ureterovesical junction obstruction, 578*f*, 579
Urethra, 633
  acquired disorders
    condylomata acuminata, 655–656
    meatal stenosis, 656
    urethral stricture, 653–655
  congenital anomalies
    anterior urethral valves, 649
    chordee without hypospadias, 651
    duplication, 646
    epispadias, 651
    hypospadias, 649–651, 650*f*
    posterior urethral valves, 646, 648*f*, 648–649
    urethral stricture, 646, 647*f*
    urethrorectal and vesicorectal fistulas, 649
  female (*See also* Female urethra disorders)
    description of, 15
    pediatric, 777
  male, 14–15
Urethral calculi, 287
Urethral caruncle, 662–663, 663*f*
Urethral catheterization
  catheter
    design of, 118, 119*f*
    difficult placement and removal of, 118
    indwelling, 118
  description of, 117
  in men, 117–118
  in women, 118
Urethral closure pressure profile, 488
Urethral dilation, 654
Urethral discharge, 43
Urethral diverticulum, 119, 664–668, 665*f*–666*f*
Urethral injuries, 302
  anterior, 304*f*–305*f*, 304–306
    clinical findings, 304–305, 305*f*
    complications, 305
    etiology, 304, 304*f*
    pathogenesis and pathology, 304
    prognosis, 306
    treatment, 305
  posterior, 302*f*–303*f*, 302–304
    clinical findings, 302, 303*f*
    complications, 303
    differential diagnosis, 302
    etiology, 302, 302*f*
    prognosis, 304
    treatment, 303*f*, 303–304
Urethral meatus, 633
Urethral pressure profile, 500
Urethral pressure profilometry, 487–488, 488*f*
Urethral probes, 124*f*
Urethral stones, 287
Urethral stricture
  complications, 654
  differential diagnosis, 654
  instrumental examination, 654
  laboratory findings, 653
  prognosis, 655
  symptoms and signs, 653
  treatment, 654–655
    dilation, 654
    surgical reconstruction, 654–655
    urethrotomy, 654
  x-ray findings, 654
Urethritis, 219–220
  acute, 661
  chronic, 661
  in HIV patients, 222–223
  in male
    clinical presentation, 244
    complications in, 244
    definition of, 244
    documentation of, 245
    etiology, 244–245
    laboratory testing, 244
    treatment, 245–246, 246*t*
  nongonococcal, 246
  persistent, 246
  recurrent, 246

Urethrography, 76*f*–78*f*
Urethrorectal fistulas, 649
Urethroscopy, 119
Urethrovaginal fistulas, 663–664
Uretic bud (UB), 18–19
Urge incontinence, 37
Urgency urinary incontinence, 504–505
Uric acid nephropathy, 546
Urinalysis, 49, 539–540
  erythrocyte casts, 539–540
  fatty casts, 540
  granular casts, 540
  macroscopic examination, 50
    appearance, 50
    bacteria and leukocytes, 51
    color, 50
    glucose, 51
    hemoglobin, 51
    pH of urine, 50
    protein levels, 50–51
    specific gravity, 50
  for male infertility evaluation, 714
  microscopic examination, 51–54, 52*f*
    bacteria, 51 (*See also* Bacteriuria)
    casts, 53–54
    crystals, 54
    erythrocytes, 52–53, 53*f*
    leukocytes, 51–52
    other findings, 54
  prostate cancer tests, 55–56
  proteinuria, 539
  urinary tract infection evaluations, 204*t,* 204–205
  urine collection, 49–50
    from children, 50
    from men, 50
    method of, 49–50
    timing of, 49
    from women, 50
  urothelial cancer tests, 55, 56*t*
Urinary diversion, 197, 391
  complications, 399
    calculi, 403
    continence and urinary function, 402–403
    metabolic and nutritional disorders, 399, 401
    pyelonephritis and renal deterioration, 403
    stoma, 401–402, 402*t*
  continent
    general considerations, 395–396
    large intestine reservoirs, 397–399, 399*f,* 400*f*
    small intestine reservoirs, 396–397, 397*f,* 398*f*
    ureterosigmoidostomy, 396, 396*f*
  intestinal conduit
    colon, 392, 394*f,* 395*f*
    ileal, 392, 393*f*
    jejunal, 392
  postoperative care, 399
  preoperative counseling and preparation, 391–392
  temporary, 197
Urinary incontinence, 402–403, 499–506
  chronic, 499
  general approach, 499–500
  mixed, 495, 505
  in multiple sclerosis, 476
  neuropathic, 506
  overflow, 505–506
  pathophysiology, 499
  prevalence, 499
  stress, 500–504
  transient, 499
  urge, 495, 504
Urinary obstruction and stasis. *See* Obstruction and stasis, urinary
Urinary retention, 37
Urinary stone. *See* Calculi
Urinary tract
  fistula of, 56
  imaging of, 63 (*See also* Radiology; *specific technique*)
  retrograde instrumentation of, 117–126
    cystoscopy, 119–120
    lasers, 125–126
    lower tract calculi removal, 125
    transurethral surgery, 123–125, 124*f*
    ultrasonography, 126, 126*f*
    ureteral catheterization, 120*f*–122*f,* 120–123
    urethral catheterization, 117–118, 119*f*
    urethroscopy, 119
Urinary tract infection (UTI), 201–223
  antibiotics for, 205
    aminoglycosides, 208
    antimicrobial agents for common uropathogens, 206*t*
    cephalosporins, 208
    dosage adjustments for liver and renal diseases, 206*t*
    fluoroquinolones, 207
    nitrofurantoin, 207–208
    penicillins, 208
    probiotics, 209
    prophylactic regimens, 207*t*
    resistance to, 208–209
    selection of, principles for, 205
    trimethoprim–sulfamethoxazole, 206–207
    by type of infection, 207*t*
  causative pathogens, 203–204
  clinical presentation of
    bladder infection, 216–217
    epididymitis/orchitis, 220–221
    kidney infection, 209–216
    prostate infection, 217–219
    urethritis, 219–220
  in diabetes mellitus, 223
  diagnosis of, 204–205
    localization studies, 205, 205*f*
    urinalysis, 204*t,* 204–205
    urine culture, 204*t,* 205
  epidemiology of, 201–202, 202*t*
  in HIV/AIDS, 222–223
  incidence of, 201–202
  pathogenesis of
    bacterial entry, 202
    bacterial pathogenic factors in, 203
    host factors, 202–203
  pregnancy and, 221–222, 222*t*
  after renal transplantation, 569
  risk factors for, 201
Urine
  bloody, 37–38
  cloudy, 37
Urine cortisol, 513

Urine culture, for urinary tract infection, 204*t*, 205
Urine cytology, 55
Urine pooling, 777
Urinoma, 139
Urodynamics
  abdominal leak point pressure, 494
  components of, 485–492
  cystometry (*See* Cystometry)
  definition of, 485
  detrusor external sphincter dyssynergia, 493–495
  detrusor leak point pressure, 494
  electromyography, 488
  emptying phase of, 485
  filling phase of, 490*f*–491*f*
  guidelines for, 486*t*
  indications for, 485, 486*t*
  lower urinary tract dysfunction assessments with, 477–478
  lower urinary tract symptoms, 496
  mixed urinary incontinence evaluations, 495
  neurogenic bladder assessments with, 478, 495–496
  overactive bladder evaluations, 495
  postvoid residual, 485–486
  storage phase of, 485
  stress-induced urinary incontinence evaluations, 495
  urethral pressure profilometry, 487–488, 488*f*
  urgency urinary incontinence evaluations, 495
  uroflowmetry, 486–487, 487*f*
  videourodynamics, 493, 493*f*
  voiding pressure flow studies, 492*f*–493*f*, 492–493
Uroflowmetry, 486–487, 487*f*
Urogenital ridge, 24
Urogenital sinus
  description of, 27, 571
  repair of, 700*f*
Urography, 64–65, 67*f*–70*f*, 68, 71
  intravenous, 64–65, 67*f*–68*f*, 68
  percutaneous, 68, 71
  retrograde, 68, 69*f*–70*f*
Urolithiasis, 51
Urothelial cancer (UCs)
  immunotherapy for, 419
  localized, 419
  metastatic, 419
  radiotherapy for, 430
  tests for, 55
    bladder tumor antigen test, 55
    nuclear matrix protein 22 test, 55
    urine cytology, 55
UroVysion, 55, 313

V

Vaccines
  immunotherapy uses of, 417–418
  prostate cancer, 418–419
Vacuum constriction device, 620–621
Vagina, 44, 632
Vaginismus, 637*t*, 640
Vaginoplasty, 698–699, 701, 751–756, 753*t*–754*t*, 755*f*–758*f*
Valrubicin, 317
Van Buren sounds, 654
Vanishing testis syndrome, 719
Vardenafil (Levitra). *See* Phosphodiesterase type-5 inhibitors (PDE-5Is)
Varicocele
  male infertility and, 722, 724–725, 725*t*
  pediatric diagnosis of, 773
  transcatheter embolization of, 112
Varicocelectomy, laparoscopic, 157
Vas deferens, 43
Vasal aspiration, 727
Vascular interventional radiology, 107
  transcatheter embolization
    for angiomyolipoma, 111, 111*f*
    for benign prostatic hyperplasia, 107–109, 109*f*
    for bleeding sites, 107
    for high-flow priapism, 112
    for lower urinary tract hemorrhage, 109–110
    for ovarian vein varices, 112
    for pelvic congestion syndrome, 112
    for pelvic hemorrhage, 109–110
    for pseudoaneurysms, 107, 108*f*
    for renal artery aneurysms, 114
    for renal AVFs and malformations, 107
    for renal cell carcinoma, 110*f*, 110–111
    for renal function cessation, 111–112
    for varicocele, 112
Vasoseminal vesiculography, 71, 79*f*
Vasovasostomy, 725*f*, 725–726
Venous gas embolism (VGE), 150
Veress needle, 152, 152*f*, 154
Vesical allergy, 589–590
Vesical diverticula, 590, 590*f*
Vesical fistulas
  causes, 590
  diagnosis, 591*f*, 591–592
  differential diagnosis, 592
  laboratory findings, 591
  prognosis, 592
  sign and symptoms, 590
  treatment, 592
Vesical tuberculosis, 234. *See also* Tuberculosis
Vesicobulbovesical micturition reflex, 455–456
Vesicorectal fistulas, 649
Vesicospinovesical micturition reflex, 456
Vesicoureteral reflux (VUR), 191–198, 493, 493*f*. *See also* Ureterovesical junction
  causes, 192–193
    complete ureteral duplication, 193, 194*f*
    contracted bladder, 194
    ectopic ureteral orifice, 193
    resection of ureterocele, 194–195
    trigonal weakness, 193
    ureteral meatotomy, 194
    ureterocele, 193
    voiding dysfunction, 194
  clinical findings, 195–196
    hypertension, 195
    laboratory findings, 195
    physical findings, 195
    spinal cord disease, 195–196
    x-ray findings, 196
  complications
    hydroureteronephrosis, 195
    pyelonephritis, 195
  incidence, 195
  prognosis, 198

Vesicoureteral reflux (VUR) (*Cont.*):
  treatment, 196–198
    endoscopic, 197–198
    medical, 196–197
    surgical, 197–198
Vesicourethral unit, 20–23, 21*f*–23*f*
  anomalies, 24
  prostate development, 23–24
  urogenital sinus, differentiation of, 21–22
    in females, 23*f*
    in males, 22*f*
Vestibular glands, 632
Viberect, 623
Videourodynamics, 493, 493*f*
Vinblastine, 409*t*
Virchow's/Troisier's node, 46
Voiding cystourethrograms, 71
Voiding cystourethrography, posterior urethral valves, 646, 648
Voiding pressure flow studies, 492*f*–493*f*, 492–493
von Hippel–Lindau disease, 334–335, 523
Vulva, 632
Vulvar vestibule, 632

W

WAGR syndrome, 342
Waldeyer's sheath, 191, 192*f*
Warts
  diagnosis of, 252
  etiology of, 251–252
  treatment of, 252*t*, 252–253
Weddelite, 259
Whitaker test, 132–133, 133*f*, 580
Wilms tumor
  bilateral, 345
  biopsy of, 344
  chemotherapy for, 345
  clinical findings of, 344
  computed tomography of, 344
  differential diagnosis of, 344
  etiology of, 343
  familial, 342–343
  histologic findings in, 343*f*
  imaging of, 344
  incidence of, 342
  lung metastases from, 344
  needle biopsy of, 344
  nephrogenic rests associated with, 343
  neuroblastoma versus, 344
  pathogenesis of, 343
  pathology associated with, 343, 343*f*
  prognosis for, 345–346
  radiation therapy for, 345
  signs and symptoms of, 344
  staging of, 343–344
  surgery for, 345
  treatment of, 345
Wilson's disease, 548
Wolffian duct, 21
Women's sexual health
  anatomy of, 632–633
  external genitalia, 633
  female sexual dysfunction
    classification of, 636–640, 637*t*
    description of, 635–636
    female genital arousal disorder, 637*t*, 638–639
    female orgasm disorder, 637*t*, 639
    hypoactive sexual desire disorder, 636–638, 637*t*
    persistent genital arousal disorder, 637*t*, 639
    sexual pain disorders, 637*t*, 640
  female sexual response, 631–632, 632*f*, 632*t*
  in pregnancy, 634
  sexual wellness, 631, 633–635
World Professional Association for Transgender Health (WPATH), 749
Wuchereria bancrofti, 239

X

Xanthogranulomatous pyelonephritis (XGP), 212–215, 214*f*, 270
  management, 215
  presentation and findings, 213
  radiographic imaging, 213–215, 214*f*
46,XX DSD, 685
XX male syndrome, 719
XX sex reversal, 678*t*
XYY syndrome, 719

Y

Y chromosome microdeletion analysis, 713
Yohimbine, 619
Young syndrome, 723

Z

Zika virus, 255